Official Title: A Phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy and Safety of Obinutuzumab in Patients with Systemic Lupus Erythematosus

NCT Number: NCT04963296

Document Date: Protocol Amendment Version 4: 29-Sep-2023

PROTOCOL

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS**
PROTOCOL NUMBER:	CA42750
STUDY NAME	ALLEGORY
VERSION NUMBER:	*4*
TEST COMPOUND:	Obinutuzumab (RO5072759)
STUDY PHASE:	Phase III
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 125054 EU CT Number: 2023-504774-38-00 EudraCT Number: 2020-005760-57 NCT Number: NCT04963296
SPONSOR NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	*See electronic signature and date stamp on the final page of this document.*
3	See electronic signature and date stamp on the final page of this document.
2	31 March 2022
1	19 February 2021

PROTOCOL AMENDMENT, VERSION 4

RATIONALE

Protocol CA42750, Version 4, has been amended to simplify the laboratory assessments conducted during the open-label period of the study, modify the open-label dosing schedule, add an additional pregnancy test prior to open-label dosing, add an exploratory endpoint, and to clarify additional aspects of the trial. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The study schema has been updated to reflect the modified dosing regimen in the open-label period of the study (Section 1.2). Specifically, the obinutuzumab infusion visit at Week 80 has been removed and an obinutuzumab infusion visit has been added at Week 104, six months after the Week 78 infusion.
- The Schedule of Activities (SOA) for Blinded Treatment has been updated to include pregnancy testing at the Week 52 visit, which will help support decision-making for participant disposition following completion of the blinded treatment period (Section 1.3, Table 1).
- The SOA for Open-Label Treatment has been updated to reflect the modified dosing regimen, with removal of the open-label obinutuzumab infusion at Week 80 and addition of an open-label obinutuzumab infusion at Week 104 (Section 1.3, Table 2).
- An additional exploratory endpoint evaluating annualized BILAG flare rate has been added to better describe how people with lupus feel, function, and survive (Sections 3 (Table 4), and 9.4.3.2).
- The description of open-label treatment has been updated to reflect the modified dosing regimen, with removal of the open-label obinutuzumab infusion at Week 80 and addition of an open-label obinutuzumab infusion at Week 104 (Sections 4.1.3, 6.1.1, and 6.1.3).
- A paragraph describing the management of participants treated per previous versions of the SOA for Open-Label Treatment has been added to provide guidance and ensure that all participants receiving OLT receive a total of four obinutuzumab infusions during their open-label participation (Sections 4.1.3 and 4.5).
- It has been indicated that the Medical Monitor may be consulted if there are any questions related to eligibility criteria (Section 5.1).
- The concomitant medication section has been updated to include more generic wording giving permission to record medications used by a patient more than 7 days prior to screening in the Concomitant Medications eCRF (e.g., COVID-19 vaccinations and latent TB treatment) (Section 6.8).
- It has been made explicit that expedited safety reports are provided to EudraVigilance (Section 8.3.4).
- Definition of B-Cell depletion has been updated (Appendix 6).

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS**
PROTOCOL NUMBER:	CA42750
STUDY NAME:	ALLEGORY
VERSION NUMBER:	4
TEST COMPOUND:	Obinutuzumab (RO5072759)
SPONSOR NAME:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local monitor.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 125054 EU CT Number: 2023-504774-38-00 EudraCT Number: 2020-005760-57 NCT Number: NCT04963296

STUDY RATIONALE

This is a parallel-group, double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of obinutuzumab versus placebo among participants with active, autoantibody-positive systemic lupus erythematosus (SLE) treated with standard-of-care therapy.

OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of obinutuzumab compared with placebo in participants with SLE when added to standard-of-care oral therapies. Specific primary and secondary objectives and corresponding endpoints for the study are outlined below.

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of obinutuzumab compared with placebo	• Proportion of participants who achieve SRI(4) at Week 52, where SRI(4) is defined as achievement of all of the following: – Reduction from baseline of ≥4 points in the SLEDAI-2K – No new systems or organs affected, as defined by ≥1 new BILAG A or ≥2 new BILAG B items compared with baseline using BILAG-2004 – No worsening from baseline of ≥0.30 points on a 3-point PGA-VAS

Key Secondary Objectives	Corresponding Endpoint
• To evaluate the efficacy of obinutuzumab compared with placebo	• Proportion of participants who achieve SRI(6) at Week 52, where achieving SRI(6) is defined as all of the following: – Reduction from baseline of ≥6 points in the SLEDAI-2K – No new systems or organs affected, as defined by ≥1 new BILAG A or ≥2 new BILAG B items compared with baseline using BILAG-2004 – No worsening from baseline of ≥0.30 points on a 3-point PGA-VAS • Proportion of participants entering the study on prednisone ≥ 10 mg/day (or equivalent) who achieve Sustained Corticosteroid Control from Week 40 through Week 52, which requires all of the following: – No treatment with prednisone > 7.5 mg/day (or equivalent) from Week 40 through Week 52 – No receipt of intravenous, intramuscular, or intra-articular corticosteroids from Week 40 through Week 52 • Time to first BILAG flare over 52 weeks, where flare is defined as the occurrence of ≥ 1 new BILAG A or ≥ 2 new BILAG B manifestations from the previous visit • Proportion of participants who achieve Sustained SRI(4) response from Week 40 through Week 52, where achieving Sustained SRI(4) response is defined by achievement of SRI(4) from Week 40 through Week 52 • Proportion of participants who achieve BICLA at Week 52, where achieving BICLA is defined as <u>all</u> of the following: – Reduction of all baseline BILAG-2004 A items to B/C/D and baseline BILAG-2004 B items to C/D – No new systems or organs affected, as defined by ≥1 new BILAG A or ≥2 new BILAG B items compared with baseline – No net increase in SLEDAI-2K score from baseline – No worsening from baseline of ≥0.30 points on a 3-point PGA-VAS

BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; PGA = Physician's Global Assessment; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI = Systemic Lupus Erythematosus Responder Index; VAS = Visual Analog Scale.

Other Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of obinutuzumab compared with placebo	• Proportion of participants who achieve SRI(4) at Week 24 • Proportion of participants who achieve clinical SRI(4) at Week 52, where clinical SRI(4) is defined as SRI(4) excluding consideration of laboratory SLEDAI-2K items • Proportion of participants who achieve SRI(4) at Week 52 on low-dose corticosteroids, defined as prednisone ≤7.5 mg/day (or equivalent) • Proportion of participants who achieve LLDAS at Week 52, where LLDAS is defined as achievement of <u>all</u> of the following: – SLEDAI-2K ≤ 4 – No SLEDAI-2K activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no BILAG hemolytic anemia or gastrointestinal activity – No new SLEDAI-2K activity compared with the previous assessment – PGA-VAS ≤1 – Current prednisone dose ≤ 7.5 mg/day (or equivalent) • Proportion of participants who achieve DORIS at Week 52, where DORIS is defined as achievement of all of the following: – Clinical SLEDAI-2K = 0 – PGA-VAS < 0.5 – Current prednisone dose ≤ 5 mg/day (or equivalent) • Change in FACIT-F scale from baseline to Week 24 and from baseline to Week 52 • Change in SF-36 v2 Bodily Pain domain scale from baseline to Week 24 and from baseline to Week 52 • Change in SF-36 v2 Physical Component Summary scale from baseline to Week 24 and from baseline to Week 52

BILAG = British Isles Lupus Assessment Group; DORIS = Definition of Remission in SLE; FACIT-F = Functional Assessment of Chronic Illness Therapy−Fatigue; LLDAS = Lupus Low Disease Activity State; PGA = Physician's Global Assessment; SF-36 v2 = 36-Item Short Form Survey, Version 2; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI = Systemic Lupus Erythematosus Responder Index; VAS = Visual Analog Scale.

Other Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of obinutuzumab compared with placebo	• Change in active joint count (swollen plus tender) from baseline to Week 24 and from baseline to Week 52 • Proportion of participants who achieve a ≥ 50% reduction in active joint counts (swollen plus tender) at each study visit, among participants with ≥ 4 active joints at baseline • Proportion of participants who achieve a ≥ 50% reduction in CLASI Total Activity Score at each study visit, among participants with CLASI Total Activity Score ≥ 10 at baseline • Proportion of participants who achieve sustained corticosteroid control from Week 40 through Week 52, which requires all of the following: – No treatment with prednisone > 5 mg/day (or equivalent) from Week 40 through Week 52 – No receipt of intravenous, intramuscular, or intra-articular corticosteroids from Week 40 through Week 52 • Cumulative corticosteroid use (in equivalent milligrams of prednisone) through Week 52 • *Annualized flare rate through Week 52*
• To evaluate the safety of obinutuzumab compared with placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Characterization of adverse events of special interest, including, among others, IRRs, neutropenia, infections, and thrombocytopenia • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
• To characterize the obinutuzumab PK profile	• Serum concentrations of obinutuzumab at specified timepoints
• To evaluate the immune response to obinutuzumab	• Prevalence of ADAs at baseline and incidence of ADAs during the study (only for participants treated with obinutuzumab)

ADA = anti-drug antibody; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity; IRR = infusion-related reaction; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic.

OVERALL DESIGN AND STUDY POPULATION

This is a parallel-group, double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of obinutuzumab versus placebo among participants with active, autoantibody-positive SLE treated with standard-of-care therapy.

Participants must be 18–75 years of age and have SLE as assessed using the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria at screening. Participants must have current autoantibody positivity (anti-nuclear antibody, anti-double-stranded DNA, and/or anti-Smith) and low complement (low C3 and/or low C4 and/or low CH50) at screening. Participants must have a high degree of disease activity, as defined by a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of ≥8 excluding points for alopecia, headache, and fever; and ≥1 British Isles Lupus Assessment Group (BILAG) Category A manifestation or ≥2 Category B manifestations. There are additional protocol-specific requirements for specific SLEDAI-2K items for determination of eligibility. Participants must also be receiving one or more standard therapies for SLE at a stable dose at

the time of randomization. Key exclusion criteria include severe lupus nephritis (LN); active, severe CNS lupus; evidence of active infection; and other safety-related exclusions.

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult patients
Control Method:	Placebo	**Population Diagnosis or Condition:**	Active, autoantibody positive systemic lupus erythematosus treated with standard of care therapy.
Interventional Model:	Parallel group	**Population Age:**	18–75 years
Test Compound:	Obinutuzumab (RO5072759)	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	Approximately 300

STUDY TREATMENT

The investigational medicinal product (IMP) for this study is obinutuzumab and placebo.

Participants will be randomized to receive obinutuzumab 1000 mg IV infusions or placebo on Day 1 and at Weeks 2, 24, and 26 of blinded treatment. During open-label treatment (OLT), participants will receive obinutuzumab 1000 mg IV infusions at Weeks 54, 56, 78, and *104*. All infusions (blinded and open-label) will be preceded by the following premedications:

- Methylprednisolone: 80 mg IV and
- Acetaminophen/paracetamol: 650–1000 mg PO or intravenously and
- Diphenhydramine: 50 mg PO or intravenously or equivalent dose of similar agent

DURATION OF PARTICIPATION

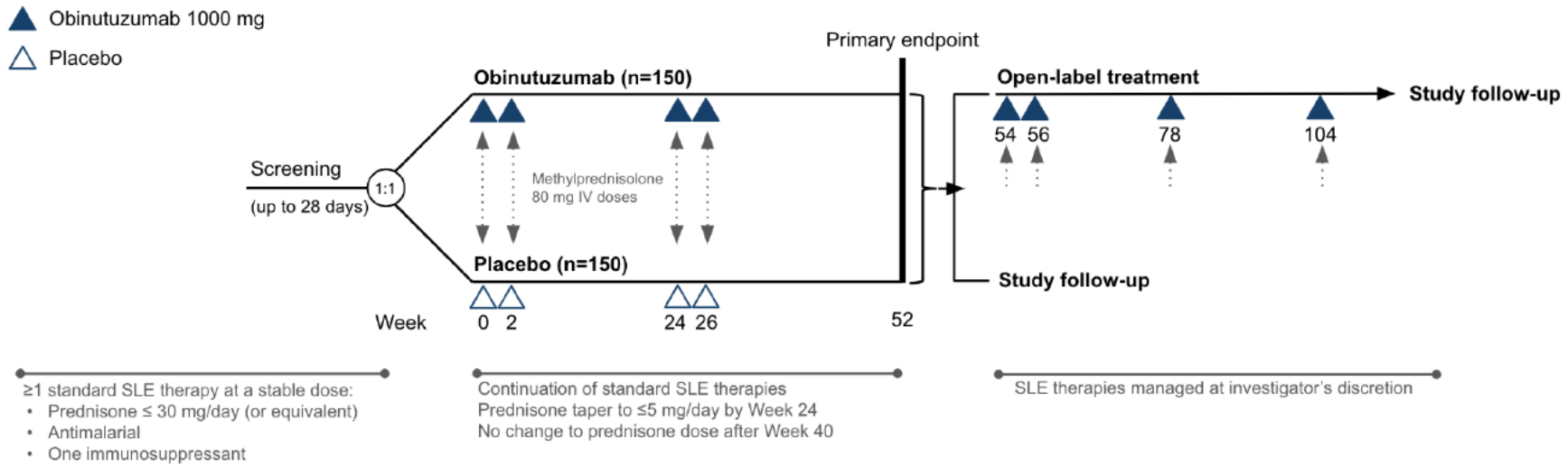
The planned duration of study participation for each individual is at least 1.5 years (18 months), which includes 12 months of blinded treatment and 6 additional months of SFU if OLT is not given. Participants who receive OLT will receive an additional *18* months of OLT, for a total duration of study participation of *3* years (*36* months). Additional SFU may be required if persistent B-cell depletion is present.

COMMITTEES

Independent Committees:	Independent Data Monitoring Committee
Other Committees:	Not applicable

1.2 STUDY SCHEMA

Figure 1 Study Schema



SLE = systemic lupus erythematosus.

1.3 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities for Blinded Treatment

	Scr. [a]	Day 1	Blinded Treatment Visits															Unsch. Visit [b]	Early Study Discont.
Week	−4 to −1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	NA	NA
Study Day(s)	−28 to −1	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364	NA	NA
Informed consent [a]	x																		
IxRS [a]	x	x	x						x	x							x		x
Inclusion/exclusion criteria	x	x																	
Demographic data	x																		
Medical history and baseline conditions	x	x																	
PROs [c]		x				x			x				x				x	x	x
Disease activity assessments [d]	x	x		x	x	x	x	x	x		x	x	x	x	x	x	x	x	x
Vital signs [e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Complete physical examination [f]	x																		
Limited physical examination [g]		x		x	x	x	x	x	x		x	x	x	x	x	x	x	x	x
Chest X-ray [h]	x																		
ECG (12-lead)	x																		
Hematology [i]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry [j]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urinalysis [k]	x	x		x	x	x	x	x	x		x	x	x	x	x	x	x	x	x
Pregnancy test [l]	x	x	x						x	x							*x*		

Table 1 Schedule of Activities for Blinded Treatment (cont.)

	Scr. [a]	Day 1	Blinded Treatment Visits															Unsch. Visit [b]	Early Study Discont.
Week	−4 to −1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	NA	NA
Study Day(s)	−28 to −1	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364	NA	NA
HBsAg, HBcAb, HCV serology [m]	x																		
HBV DNA and HCV RNA		See footnote m																	
Quantitative serum Ig levels		x				x			x				x				x		x
Vaccination antibody titers [n]		x															x		x
Blood sample for flow cytometry	x	x	x	x		x			x				x				x	x	x
Blood sample for HSFC		x	x	x		x			x				x				x	x	x
Complement (C3, C4, and CH50)	x	x		x	x	x	x	x	x		x	x	x	x	x	x	x	x	x
Autoantibody profile [o]	x	x		x	x	x	x	x	x		x	x	x	x	x	x	x	x	x
Antiphospholipid antibodies [p]		x				x			x								x		
Serum PK sample [q]		x	x	x		x			x	x			x				x	x	x
Serum ADA sample		x	x	x		x			x	x							x	x	x
Plasma sample for biomarkers		x							x				x				x	x	x
Serum sample for biomarkers		x		x		x			x				x				x	x	x
DNA sample (optional) [r]		x																	
RNA sample for biomarkers		x		x		x			x				x				x	x	x
Concomitant medications [s]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Table 1 Schedule of Activities for Blinded Treatment (cont.)

	Scr. [a]	Day 1	Blinded Treatment Visits															Unsch. Visit [b]	Early Study Discont.
Week	−4 to −1	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	52	NA	NA
Study Day(s)	−28 to −1	1	14	28	56	84	112	140	168	182	196	224	252	280	308	336	364	NA	NA
Adverse events [t]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blinded obinutuzumab or placebo administration [u]		x	x						x	x									

ADA = anti-drug antibody; ANA = anti-nuclear antibody; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity; ClinRO = clinician-reported outcome; Discont. = discontinuation; dsDNA = double-stranded DNA; eCRF = electronic Case Report Form; EDAA = Eligibility Disease Activity Assessment; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HSFC = high-sensitivity flow cytometry; IxRS = interactive web response system; NA = not applicable; PGA = Physician's Global Assessment; PK = pharmacokinetic; PO = by mouth; PRO = patient-reported outcome; RBR = Research Biosample Repository; RNP = ribonucleoprotein; Scr. = screening; SF-36 v2 = 36-Item Short Form Survey, Version 2; SGA = Subject's Global Assessment; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; Sm = Smith; SSA (Ro) = Sjogren's Syndrome A; SSB (La) = Sjogren's Syndrome B; TB = tuberculosis; UPCR = urinary protein-to-creatinine ratio; Unsch. = unscheduled.

Notes: On treatment days, all assessments, including blood collection, should be performed prior to any protocol-mandated intervention, i.e. prior to premedications, unless otherwise specified. Visits except for Day 1 should be performed within ± 3 days of the scheduled visit.

If available according to local policy, mobile nursing may be used for assessments that do not require infusions, efficacy evaluations, or planned treatment changes. The following visits are not eligible for mobile nursing: screening, Day 1, Weeks 2, 24, 26, and 52; early study discontinuation; and unscheduled visits.

[a] At screening, IxRS will be contacted to obtain assignment of participant screening number. On Day 1, sites will contact the IxRS to obtain a participant's randomization number and drug assignment. Informed consent must be documented before any study-specific screening procedure is performed and may be obtained more than 28 days before initiation of study treatment. The screening period begins on the day the first screening procedure is performed. At the discretion of the investigator following consultation with the Medical Monitor, the screening window may be extended by up to 7 additional days to permit completion of participant eligibility assessment. At screening, testing for HIV and/or TB will be performed locally if required by local regulations.

[b] Hematology, chemistry and/or urinalysis assessments should be performed as part of unscheduled visits only if clinically indicated (e.g. if the unscheduled visit is being done as part of an assessment of an adverse event for which such labs would be relevant) or if meeting the following criteria: ClinROs, PROs, as well as blood and/or urine assessments should only be performed as part of unscheduled visits if these were

Table 1 Schedule of Activities for Blinded Treatment (cont.)

specified to be performed as part of the previously scheduled visit but were not performed for any reason, or if clinically appropriate in the judgment of the investigator.

[c] PROs are FACIT-F, SF-36 v2, EQ-5D-5L, and SGA. These will be completed prior to other assessments and procedures by the participant.

[d] Disease activity assessments (also referred to as ClinRO assessments) are tender/swollen joint counts; CLASI, SLEDAI-2K, BILAG-2004 Index, and PGA.

At screening and on Day 1, following completion of the aforementioned ClinRO assessments, the EDAA will also be completed to assist in eligibility determination. The EDAA is a modified version of SLEDAI-2K that contains the additional scoring requirements described in Section 5.1. Participants must have an EDAA total activity score of ≥8 at screening and Day 1 to be considered eligible for enrollment.

At screening only, the investigator should refer to the domain-specific algorithms in the BILAG-2004 Index scoring guidance (see Appendix 14) upon completion of the BILAG-2004 Index to assign Category A and/or B grades to applicable domains for eligibility determination. All other visits involving BILAG-2004 assessment only require completion of the BILAG-2004 Index (with the Sponsor responsible for assigning domain-specific category grades upon receipt of data recorded on the BILAG-2004 Index).

[e] Vital signs include blood pressure and pulse rate (while participant is seated for 5 minutes), respiratory rate, and body temperature. Vital signs should be taken pre-infusion, then in seated or semi-supine position, every 15 minutes for 1 hour, then every 30 minutes until the end of the infusion, and within 30 minutes post-infusion. Additional readings may be obtained at the discretion of the investigator.

[f] A complete physical examination at screening should include measurement of height and weight; and evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

[g] The limited physical exam will include the organ systems required to complete SLE disease activity assessments. Additional symptom-directed physical examinations should be performed as clinically indicated. Changes from baseline abnormalities should be recorded. New or worsened clinically significant abnormalities should be recorded as SLE disease activity or adverse events as appropriate.

[h] If a chest X-ray has been obtained within the past 3 months and no clinically significant abnormality was observed and no new pulmonary signs or symptoms are exhibited, no chest X-ray is required.

[i] Hematology includes CBC, RBC count, WBC count and differential, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and quantitative platelet count.

[j] Serum chemistry panel includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, albumin, cholesterol, total bilirubin, BUN, uric acid, creatinine, random glucose, lactate dehydrogenase, potassium, sodium, chloride, calcium, phosphorus, CPK, and triglycerides.

[k] First morning urine sample is preferred. All urinalyses including dipstick (pH, specific gravity, glucose, protein, ketones, and blood), microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria), macroscopic urinalysis, and UPCR will be analyzed at the central laboratory.

[l] For women of childbearing potential, including those who have had a tubal ligation: a negative urine pregnancy test is required at screening and prior to all study drug infusions. Urine pregnancy tests will be performed at subsequent visits prior to obinutuzumab/placebo treatment. If urine

Table 1 Schedule of Activities for Blinded Treatment (cont.)

test is positive, results will be confirmed with a serum pregnancy test prior to study drug administration. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[m] Participants who are HBsAg negative and HBcAb positive require monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo. Participants with positive HCV antibody test result require monthly HCV RNA monitoring until 12 months after the final dose of obinutuzumab or placebo.

[n] Antibody titers or semi-quantitative measurements include mumps, rubella, Varicella, tetanus, influenza, and S. pneumoniae, as available per laboratory facility.

[o] Autoantibodies include ANA, anti-dsDNA, anti-Sm, anti-SSA (Ro), anti-SSB (La), and anti-RNP.

[p] Antiphospholipid antibodies include anti-cardiolipin and anti-beta-2-glycoprotein antibodies.

[q] At infusion visits, obtain pre-infusion (recommended to be collected in parallel with the earlier blood draw [prior to premedication] for the sake of participant comfort) and at the end of infusion (or within 30 minutes after the end of infusion). The timing of the PK sampling pre- and post-infusion should be precisely recorded. At non-infusion visits, a single sample will be obtained.

[r] The DNA samples are optional and should only be obtained from participants who sign the separate RBR Informed Consent Form. Preferably, samples will be obtained at baseline visit, but they may be obtained at subsequent study visits.

[s] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. *Under certain circumstances, the Medical Monitor may assess that medications used by a patient more than 7 days prior to screening may need to be captured on the Concomitant Medications eCRF (e.g. COVID-19 vaccinations and latent TB treatment must always be captured on the Concomitant Medications eCRF).*

[t] On Day 1, adverse events will be recorded during infusion and post-infusion. For subsequent infusion visits, adverse events will be recorded pre-infusion, during infusion, and post-infusion. For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset.

[u] At infusion visits, premedication with methylprednisolone 80 mg IV, acetaminophen/paracetamol 650–1000 mg PO or intravenously, and diphenhydramine 50 mg PO or intravenously (or equivalent dose of a similar agent) will be given. The administration of these premedications should be completed between 30 and 60 minutes prior to the study drug infusion.

Table 2 Schedule of Activities for Open-Label Treatment

	Open-Label Treatment Visits							Unscheduled Visit [a]	Early Study Discont.
Week	54	56	58	66	78	90	*104*	NA	NA
Study Day	378	392	406	462	546	630	*728*	NA	NA
Assessment of eligibility for OLT [b]	x								
IxRS	x [c]	x			x		*x*		x
PROs [d]	x				x		*x*	x	x
Disease activity assessments [e]	x		x	x	x	x	*x*	x	x
Vital signs [f]	x	x	x	x	x	x	*x*	x	x
Limited physical examination [g]	x		x	x	x	x	*x*	x	x
Hematology [h]	x	x	x	x	x	x	*x*	x	x
Chemistry [i]	x	x	x	x	x	x	*x*	x	x
Pregnancy test [j]	x	x			x		*x*		
Urinalysis [k]	x		x	x	x	x	*x*	x	x
HBsAg, HBcAb, HCV serology [l]	x								
HBV DNA and HCV RNA	See footnote l.								
Quantitative serum Ig levels							*x*		x
Vaccination antibody titers [m]							*x*		x
Blood sample for flow cytometry					x		*x*	x	x
Blood sample for HSFC					*x*		*x*	x	x
Complement (C3, C4, and CH50)			x	x	x	x	*x*	x	x
Autoantibody profile [n]			x	x	x	x	*x*	x	x
Antiphospholipid antibodies [o]						x	*x*		
Serum PK sample [p]	*x*	x	x	x	x	x	*x*	x	x

Table 2 Schedule of Activities for Open-Label Treatment (cont.)

	Open-Label Treatment Visits							Unscheduled Visit [a]	Early Study Discont.
Week	54	56	58	66	78	90	*104*	NA	NA
Study Day	378	392	406	462	546	630	*728*	NA	NA
Serum ADA sample		x			x		*x*	x	x
Plasma sample for biomarkers							*x*		
Serum sample for biomarkers							*x*	x	
RNA sample for biomarkers							*x*		
Concomitant medications [q]	x	x	x	x	x	x	*x*	x	x
Adverse events [r]	x	x	x	x	x	x	*x*	x	x
Obinutuzumab administration [s]	x	x			x		*x*		

Table 2 Schedule of Activities for Open-Label Treatment(cont.)

ADA = anti-drug antibody; ANA = anti-nuclear antibody; BILAG = British Isles Lupus Assessment Group; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity; Discont. = discontinuation; dsDNA = double stranded DNA; eCRF = electronic Case Report Form; EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; FACIT-F = Functional Assessment of Chronic Illness Therapy-Fatigue; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HSFC = high-sensitivity flow cytometry; IxRS = interactive web response system; NA = not applicable; OLT = open-label treatment; PGA = Physician's Global Assessment; PK = pharmacokinetic; PO = by mouth; PRO = patient-reported outcome; RBR = Research Biosample Repository; RNP = ribonucleoprotein; SF-36 v2 = 36-Item Short Form Survey, Version 2; SGA = Subject's Global Assessment; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; Sm = Smith; SSA (Ro) = Sjogren's Syndrome A; SSB (La) = Sjogren's Syndrome B; UPCR = urinary protein-to-creatinine ratio.

Notes: On treatment days, all assessments, including blood collection, should be performed prior to any protocol-mandated intervention, i.e. prior to premedications, unless otherwise specified. All visits should be performed within ±3 days of the scheduled visit.

If available according to local policy, mobile nursing may be used for assessments that do not require infusions, efficacy evaluations, or planned treatment changes. The following visits are not eligible for mobile nursing: Weeks 54, 56, 78, and 104; early study discontinuation, and unscheduled visits.

[a] Hematology, chemistry and/or urinalysis assessments should be performed as part of unscheduled visits only if clinically indicated (e.g. if the unscheduled visit is being done as part of an assessment of an adverse event for which such labs would be relevant) or if meeting the following criteria: ClinROs, PROs, as well as blood and/or urine assessments should only be performed as part of unscheduled visits if these were specified to be performed as part of the previously scheduled visit but were not performed for any reason, or if clinically appropriate in the judgment of the investigator.

[b] Participants who have persistent disease activity or are at high risk for flare after completing blinded treatment may be eligible to receive OLT. Refer to Section 4.1.3 for details.

[c] At this visit, IxRS will be contacted to confirm the start of OLT.

[d] PROs are FACIT-F, SF-36 v2, EQ-5D-5L, and SGA. These will be completed prior to other assessments and procedures by the participant.

[e] Disease activity assessments are tender/swollen joint counts, CLASI, SLEDAI-2K, BILAG-2004 Index, and PGA.

[f] Vital signs include blood pressure and pulse rate (while participant is seated for 5 minutes), respiratory rate, and body temperature. Vital signs should be taken pre-infusion, then in seated or semi-supine position, every 15 minutes for 1 hour, then every 30 minutes until the end of the infusion, and within 30 minutes post-infusion. Additional readings may be obtained at the discretion of the investigator.

[g] The limited physical exam will include the organ systems required to complete SLE disease activity assessments. Additional symptom-directed physical examinations should be performed as clinically indicated. Changes from baseline abnormalities should be recorded. New or worsened clinically significant abnormalities should be recorded as SLE disease activity or adverse events as appropriate.

Table 2 Schedule of Activities for Open-Label Treatment(cont.)

[h] Hematology includes CBC, RBC count, WBC count and differential, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and quantitative platelet count.

[i] Serum chemistry panel includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, albumin, cholesterol, total bilirubin, BUN, uric acid, creatinine, random glucose, lactate dehydrogenase, potassium, sodium, chloride, calcium, phosphorus, CPK, and triglycerides.

[j] For women of childbearing potential, including those who have had a tubal ligation: a negative urine pregnancy test is required prior to all study drug infusions. If a urine test is positive, results will be confirmed with a serum pregnancy test prior to study drug administration. Study drug infusion must not be administered unless the serum pregnancy test result is negative.

[k] First morning urine sample is preferred. All urinalyses including dipstick (pH, specific gravity, glucose, protein, ketones, and blood), microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria), macroscopic urinalysis, and UPCR will be analyzed at the central laboratory.

[l] Participants who are HBsAg negative and HBcAb positive require monthly HBV DNA monitoring until 12 months after the final dose of obinutuzumab or placebo. Participants with positive HCV antibody test result require monthly HCV RNA monitoring until 12 months after the final dose of obinutuzumab or placebo.

[m] Antibody titers or semi-quantitative measurements include mumps, rubella, Varicella, tetanus, influenza, and S. pneumoniae, as available per laboratory facility.

[n] Autoantibodies include anti-dsDNA *antibody.*

[o] Antiphospholipid antibodies include anti-cardiolipin and anti-beta-2-glycoprotein antibodies.

[p] At infusion visits, obtain pre-infusion (recommended to be collected simultaneously with the earlier blood draw [prior to premedication] for the sake of participant comfort) and at the end of infusion (or within 30 minutes after the end of infusion). The timing of the PK sampling pre- and post-infusion should be precisely recorded. At non-infusion visits, a single sample will be obtained.

[q] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. *COVID-19 vaccinations must always be captured on the Concomitant Medications eCRF.*

[r] For subsequent infusion visits, adverse events will be recorded pre-infusion, during infusion, and post-infusion. For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset.

[s] At infusion visits, premedication with methylprednisolone 80 mg IV, acetaminophen/paracetamol 650–1000 mg PO or intravenously, and diphenhydramine 50 mg PO or intravenously (or equivalent dose of a similar agent) will be

Table 2 Schedule of Activities for Open-Label Treatment(cont.)

given. The administration of all premedications should be completed between 30 and 60 minutes prior to the study drug infusion. *Participants who received open-label obinutuzumab according to the Schedule of Activities for OLT in earlier versions (1,2, and 3) of the protocol, which involved administration of the last OLT infusion at Week 80, will complete remaining OLT visits according to the same version of the SOA for OLT that was initially followed, and then proceed to SFU. As such, no further open-label obinutuzumab infusions will be administered for any participants who received a dose at Week 80.*

Table 3 Schedule of Activities for Study Follow-Up

	Study Follow-Up Visits		Unscheduled Visit	Study Discontinuation
Week [a] (Week if OLT given)	78 (130)	Every 26 weeks thereafter (if required) [b]	NA	
Study Day (Study Day if OLT given)	546 (910)			
Vital signs c	x	x	x	x
Hematology [d]	x	x	x	x
Chemistry [e]	x	x	x	x
HBV DNA and HCV RNA	See footnote f.			
Quantitative serum Ig levels	x	x		x
Blood sample for flow cytometry	x	x		x
Concomitant medications [g]	x	x	x	x
Adverse events [h]	x	x	x	x

eCRF = electronic Case Report Form; HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; NA = not applicable; OLT = open-label treatment; SFU = study follow-up; UPCR = urinary protein-to-creatinine ratio.

Notes:. All visits should be performed within ±7 days of the scheduled visit.

Notes: If available according to local policy, mobile nursing may be used for assessments that do not require infusions, efficacy evaluations, or planned treatment changes. The following are not eligible for mobile nursing: unscheduled and study discontinuation visits.

[a] The first SFU visit will be scheduled approximately six months after the previous study visit: for participants who do not enter OLT after blinded treatment (last visit Week 52), the first SFU visit will occur on Week 78. For participants who receive OLT (last visit Week *130*), the first SFU visit will occur at Week *156*.

[b] At least one SFU visit is required for all participants. Additional SFU may be required for participants with persistent B-cell depletion. Refer to Section 4.1.4.

[c] Vital signs include blood pressure and pulse rate (while participant is seated for 5 minutes), respiratory rate, and body temperature. Additional readings may be obtained at the discretion of the investigator.

[d] Hematology includes CBC, RBC count, WBC count and differential, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and quantitative platelet count.

Table 3 Schedule of Activities for Study Follow-Up (cont.)

[e] Serum chemistries include AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, albumin, cholesterol, total bilirubin, BUN, uric acid, creatinine, random glucose, lactate dehydrogenase, potassium, sodium, chloride, calcium, and phosphorus, CPK, and triglycerides.

[f] Participants who are HBsAg negative and HBcAb positive require monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo. Participants with positive HCV antibody test result require monthly HCV RNA monitoring until 12 months after the final dose of obinutuzumab or placebo.

[g] Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 7 days prior to screening to the study completion/discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

[h] For all serious infectious adverse events reported, CBC with differential, quantitative immunoglobulins, and flow cytometry should be measured within 1 week of onset.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to assess the efficacy and safety of obinutuzumab combined with standard-of-care therapy in participants with active systemic lupus erythematosus (SLE). Currently, there is only one approved targeted therapy for the treatment of SLE, belimumab, and there remains a need for treatments with better benefit–risk profiles that improve the long-term prognosis of patients with SLE.

2.2 BACKGROUND

2.2.1 Background on Systemic Lupus Erythematosus

SLE is an autoimmune rheumatic disease that occurs primarily in women of childbearing age. It is characterized by multisystem involvement and immunological abnormalities, and much of the tissue damage is thought to occur through autoantibody formation and immune complex deposition. The unmet medical need in SLE is high; only two new medications have been approved in more than 50 years (Burness and McCormack 2011; Deeks 2021). Current standard-of-care therapies for SLE include corticosteroids, the antimalarial therapies hydroxychloroquine, chloroquine, and quinacrine; and conventional immunosuppressants such as mycophenolate mofetil (MMF), azathioprine, and methotrexate. These agents generally have incomplete efficacy for inflammatory manifestations of SLE and their use is frequently limited by toxicities. Corticosteroids, for example, are effective for many of the manifestations of SLE but have significant short- and long-term adverse effects, including infections, osteoporosis, hyperglycemia, and hyperlipidemia. Despite the availability of standard-of-care therapies, patients with SLE remain at increased risk for damage accrual, cardiovascular disease, complications of therapy, and death (Cook et al. 2000; Gladman et al. 2002; Nossent et al. 2010, Lopez et al. 2012).

B cells play an active role in the pathogenesis of SLE. Autoreactive B cells recognize and present self-antigens, produce autoantibodies, secrete proinflammatory cytokines, and participate in T-cell costimulation. For this reason, they are attractive therapeutic targets in SLE, though there have been a number of failed studies evaluating agents that target B cells, B-cell activation, or B-cell survival factors, including randomized controlled trials of the Type I anti-CD20 monoclonal antibody rituximab for treatment of SLE (Study U2971g [EXPLORER]) and severe lupus nephritis (LN) (Study U2970g [LUNAR]). More recently, associations have been demonstrated in multiple cohorts between the degree and duration of B-cell depletion in SLE and the degree of clinical benefit, generating the hypothesis that a greater level of B-cell depletion may be necessary to achieve efficacy (Md Yusof et al. 2017; Gomez Mendez et al. 2018; Furie et al. 2020).

2.2.2 Background on Obinutuzumab

Obinutuzumab (GAZYVA®, GAZYVARO®) is a recombinant, monoclonal, humanized, and glycoengineered Type II CD20 antibody of the IgG1 isotype that specifically targets

the extracellular loop of the CD20 transmembrane antigen that is expressed on the surface of non-malignant and malignant pre-B and mature B lymphocytes but not on hematopoietic stem cells, pro-B cells, normal plasma cells, or other normal tissue (Mössner et al. 2010; Niederfellner et al. 2011; Klein et al. 2013).

Obinutuzumab is currently approved in multiple countries worldwide for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil; for the treatment (in combination with chemotherapy followed by monotherapy in patients achieving at least a partial remission) of adult patients with previously untreated Stage II bulky, III or IV follicular lymphoma (FL); and for the treatment (in combination with bendamustine followed by monotherapy) of patients with FL who have relapsed after, or are refractory to, a rituximab-containing regimen.

Compared with Type I anti-CD20 antibodies, obinutuzumab has greater antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis, has more direct B-cell–killing effects, and is less reliant on complement-dependent cytotoxicity (Mössner et al. 2010). Because obinutuzumab does not elicit CD20 redistribution to membrane-bound lipid rafts, obinutuzumab is also associated with reduced internalization (Reddy et al. 2017). Glycoengineering of the fragment crystallizable (Fc) portion of obinutuzumab results in a higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells and macrophages/monocytes (Mössner et al. 2010).

Obinutuzumab depletes peripheral and tissue B cells to a greater degree than rituximab, as evidenced by data in non-human primates (Mössner et al. 2010) and lupus-prone mouse models (Marinov et al. 2020). Obinutuzumab demonstrated greater in vitro B-cell cytotoxicity and activation of NK cells than rituximab in rheumatoid arthritis and SLE patient blood samples (Reddy et al. 2017).

Study WA29748 (NOBILITY) was a Phase II, randomized, placebo-controlled trial that enrolled participants with severe, proliferative LN to receive four infusions of obinutuzumab or placebo in combination with mycophenolate and corticosteroids (Furie et al. 2020). In the NOBILITY study, obinutuzumab was associated with increased achievement of complete renal response (CRR) at Week 52 (35% in the obinutuzumab group vs. 23% in the placebo group; difference, 12% [95% CI: −3 to 28], $p = 0.115$) and at Week 104 (41% in the obinutuzumab group vs. 22% in the placebo group; difference, 19% [95% CI: 3 to 35], $p = 0.026$). Obinutuzumab was also associated with greater improvements in C3, C4, and anti-double stranded DNA (dsDNA) antibody levels; estimated glomerular filtration rate (eGFR); and urine protein-to-creatinine ratio (UPCR) compared with placebo. Obinutuzumab resulted in rapid and complete peripheral B-cell depletion to a greater extent than observed with rituximab in the LUNAR study. Obinutuzumab compared with placebo was not associated with increases in serious adverse events, serious infections, or deaths through the two-year observation period. Obinutuzumab was associated with an increased rate of

non-serious infusion-related reactions (IRRs; 16% vs. 10%). There were no serious IRRs in the obinutuzumab or placebo group, and no IRRs resulted in the inability to complete the obinutuzumab infusion (following protocol-instructed management, which may have included interruption or slowing of the infusion). No new safety signals were identified (Furie et al. 2020).

In summary, obinutuzumab is a humanized, glycoengineered Type II anti-CD20 antibody with enhanced depletion of B cells from peripheral blood and tissue compared with Type I antibodies such as rituximab. Consistent with its more potent B-cell depletion, obinutuzumab was superior to rituximab for the treatment of CLL and FL when administered in combination with standard chemotherapy and is currently approved worldwide for these indications. In the NOBILITY study, obinutuzumab demonstrated rapid and complete peripheral B-cell depletion in participants with severe proliferative LN and was associated with a clinically meaningful benefit over standard-of-care therapies alone (Furie et al. 2020).

Detailed information on obinutuzumab is provided in the Obinutuzumab Immunology Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The Sponsor interprets data from the NOBILITY study to suggest that obinutuzumab in combination with standard-of-care immunosuppression may confer a clinically meaningful benefit for patients with severe LN. The current study CA42750 (ALLEGORY) is being undertaken to observe whether obinutuzumab would also have clinically meaningful benefits for SLE patients with active disease, but without severe LN, and to provide long-term data to inform the use of obinutuzumab in SLE.

In light of the clinically meaningful benefits and an acceptable safety profile observed with obinutuzumab in SLE patients with severe LN, the Sponsor is undertaking the present study to assess the efficacy and safety of obinutuzumab, a Type II anti-CD20 monoclonal antibody with enhanced B-cell depletion, to address a significant unmet medical need in patients with active, autoantibody-positive SLE.

COVID-19 Benefit–Risk Assessment

An assessment was conducted to determine whether there is any impact of the coronavirus 2019 (COVID-19) pandemic on the benefit–risk assessment of this study protocol including, but not limited to, the patient population under study and study treatments being evaluated. Based on that assessment, no impact is anticipated, and the existing safety monitoring and management guidelines and risk-mitigation measures provided in the study protocol are considered adequate.

With reference to COVID-19 vaccines, an assessment was conducted to determine whether there is any impact of the COVID-19 vaccines on the benefit-risk assessment of this study protocol. Given the mechanism of action of obinutuzumab, it is expected that

the efficacy of COVID-19 vaccines may be diminished in patients who are B-cell depleted. The investigator should use clinical judgement to decide on the most suitable timing of vaccination and, where possible, COVID-19 vaccines should be administered to patients before they start immunosuppressive therapy. COVID-19 vaccines may also be administered to participants at any time during the study provided the vaccines are non-live vaccines. If administered during the study, the COVID-19 vaccines are considered concomitant medications (see Section 6.8.5). The COVID-19 vaccines must be administered in accordance with the approved/authorized vaccine label (or equivalent) and official immunization instructions. Based on this assessment, no additional risk-mitigation measures related to COVID-19 vaccination are proposed at this time. The recommendations listed above and the current safety monitoring and management guidelines and risk-mitigation measures provided in the study protocol are considered adequate.

Refer to Appendix 6 for information on anticipated risks for obinutuzumab and risk mitigation measures, including guidelines for managing adverse events associated with obinutuzumab.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of obinutuzumab may be found in the Obinutuzumab Immunology Investigator's Brochure.

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy, safety, and pharmacokinetics of obinutuzumab compared with placebo in participants with SLE when added to standard-of-care oral therapies. Specific objectives and corresponding endpoints for the study are outlined in Table 4.

Table 4 Objectives and Corresponding Endpoints

Primary Objective	Corresponding Endpoint
• To evaluate the efficacy of obinutuzumab compared with placebo	• Proportion of participants who achieve SRI(4) at Week 52, where SRI(4) is defined as achievement of all of the following: – Reduction from baseline of ≥4 points in the SLEDAI-2K – No new systems or organs affected, as defined by ≥1 new BILAG A or ≥2 new BILAG B items compared with baseline using BILAG-2004 – No worsening from baseline of ≥0.30 points on a 3-point PGA-VAS
Key Secondary Objectives	**Corresponding Endpoint**
• To evaluate the efficacy of obinutuzumab compared with placebo	• Proportion of participants who achieve SRI(6) at Week 52, where achieving SRI(6) is defined as all of the following: – Reduction from baseline of ≥6 points in the SLEDAI-2K – No new systems or organs affected, as defined by ≥1 new BILAG A or ≥2 new BILAG B items compared with baseline using BILAG-2004 – No worsening from baseline of ≥0.30 points on a 3-point PGA-VAS • Proportion of participants entering the study on prednisone ≥10 mg/day (or equivalent) who achieve Sustained Corticosteroid Control from Week 40 through Week 52, which requires all of the following: – No treatment with prednisone >7.5 mg/day (or equivalent) from Week 40 through Week 52 – No receipt of intravenous, intramuscular, or intra-articular corticosteroids from Week 40 through Week 52 • Time to first BILAG flare over 52 weeks, where flare is defined as the occurrence of ≥1 new BILAG A or ≥2 new BILAG B manifestations from the previous visit • Proportion of participants who achieve Sustained SRI(4) response from Week 40 through Week 52, where achieving Sustained SRI(4) response is defined by achievement of SRI(4) from Week 40 through Week 52 • Proportion of participants who achieve BICLA at Week 52, where achieving BICLA is defined as <u>all</u> of the following: – Reduction of all baseline BILAG-2004 A items to B/C/D and baseline BILAG-2004 B items to C/D – No new systems or organs affected, as defined by ≥1 new BILAG A or ≥2 new BILAG B items compared with baseline – No net increase in SLEDAI-2K score from baseline – No worsening from baseline of ≥0.30 points on a 3-point PGA-VAS

BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; BILAG = British Isles Lupus Assessment Group; PGA = Physician's Global Assessment; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI = Systemic Lupus Erythematosus Responder Index; VAS = Visual Analog Scale.

Table 4 Objectives and Corresponding Endpoints (cont.)

Other Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of obinutuzumab compared with placebo	• Proportion of participants who achieve SRI(4) at Week 24 • Proportion of participants who achieve clinical SRI(4) at Week 52, where clinical SRI(4) is defined as SRI(4) excluding consideration of laboratory SLEDAI-2K items • Proportion of participants who achieve SRI(4) at Week 52 on low-dose corticosteroids, defined as prednisone ≤7.5 mg/day (or equivalent) • Proportion of participants who achieve LLDAS at Week 52, where LLDAS is defined as achievement of all of the following: – SLEDAI-2K ≤4 – No SLEDAI-2K activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no BILAG hemolytic anemia or gastrointestinal activity – No new SLEDAI-2K activity compared with the previous assessment – PGA-VAS ≤1 – Current prednisone dose ≤7.5 mg/day (or equivalent) • Proportion of participants who achieve DORIS at Week 52, where DORIS is defined as achievement of all of the following: – Clinical SLEDAI-2K =0 – PGA-VAS <0.5 – Current prednisone dose ≤5 mg/day (or equivalent) • Change in FACIT-F scale from baseline to Week 24 and from baseline to Week 52 • Change in SF-36 v2 Bodily Pain domain scale from baseline to Week 24 and from baseline to Week 52 • Change in SF-36 v2 Physical Component Summary scale from baseline to Week 24 and from baseline to Week 52

BILAG = British Isles Lupus Assessment Group; DORIS = Definition of Remission in SLE; FACIT-F = Functional Assessment of Chronic Illness Therapy−Fatigue; LLDAS = Lupus Low Disease Activity State; PGA = Physician's Global Assessment; SF-36 v2 = 36-Item Short Form Survey, Version 2; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI = Systemic Lupus Erythematosus Responder Index; VAS = Visual Analog Scale.

Table 4 Objectives and Corresponding Endpoints (cont.)

Other Secondary Objectives	Corresponding Endpoints
• To evaluate the efficacy of obinutuzumab compared with placebo	• Change in active joint count (swollen plus tender) from baseline to Week 24 and from baseline to Week 52 • Proportion of participants who achieve a ≥50% reduction in active joint counts (swollen plus tender) at each study visit, among participants with ≥4 active joints at baseline • Proportion of participants who achieve a ≥50% reduction in CLASI Total Activity Score at each study visit, among participants with CLASI Total Activity Score ≥10 at baseline • Proportion of participants who achieve sustained corticosteroid control from Week 40 through Week 52, which requires all of the following: – No treatment with prednisone >5 mg/day (or equivalent) from Week 40 through Week 52 – No receipt of intravenous, intramuscular, or intra-articular corticosteroids from Week 40 through Week 52 • Cumulative corticosteroid use (in equivalent milligrams of prednisone) through Week 52 • *Annualized flare rate through Week 52*
• To evaluate the safety of obinutuzumab compared with placebo	• Incidence and severity of adverse events, with severity determined according to NCI CTCAE v5.0 • Characterization of adverse events of special interest, including, among others, IRRs, neutropenia, infections, and thrombocytopenia • Change from baseline in targeted vital signs • Change from baseline in targeted clinical laboratory test results
• To characterize the obinutuzumab PK profile	• Serum concentrations of obinutuzumab at specified timepoints
• To evaluate the immune response to obinutuzumab	• Prevalence of ADAs at baseline and incidence of ADAs during the study (only for participants treated with obinutuzumab)

ADA = anti-drug antibody; CLASI = Cutaneous Lupus Erythematosus Disease Area and Severity; IRR = infusion-related reaction; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic.

Table 4 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To evaluate the efficacy of obinutuzumab compared with placebo	• Proportion of participants who achieve SRI(8) at Week 52, where achieving SRI(8) is defined as all of the following: – Reduction from baseline of ≥8 points in the SLEDAI-2K – No new systems or organs affected, as defined by ≥1 new BILAG A or ≥2 new BILAG B items compared with baseline using BILAG-2004 – No worsening from baseline of ≥0.30 points on a 3-point PGA-VAS • Proportion of participants who achieve the individual components of SRI, BICLA, LLDAS at Week 52 • Proportion of participants who experience intercurrent events by Week 52 • SLEDAI 2K change from baseline to Week 52 • Time to first SRI(4) response sustained over two consecutive scheduled visits • Time to first LLDAS sustained over two consecutive scheduled visits • Proportions of participants who achieve SRI(4), clinical SRI(4), SRI(6), SRI(8), BICLA, and LLDAS at each study visit • Change in anti-dsDNA titer, C3, and C4 from baseline at each study visit • Change in PGA and SGA from baseline at each study visit • Change in SF 36 v2 Mental Component Summary scale from baseline to Week 52 • Change in SF 36 v2 Physical Functioning, Role Physical, Role Emotional, General Health, Vitality, Social Functioning, Mental Health domain scales from baseline to Week 52

BICLA = British Isles Lupus Assessment Group-based Composite Lupus Assessment; dsDNA = double-stranded DNA; LLDAS = Lupus Low Disease Activity State; PGA = Physician's Global Assessment; SF-36 v2 = 36-Item Short Form Survey, Version 2; SGA = Subject's Global Assessment; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000; SRI = Systemic Lupus Erythematosus Responder Index.

Table 4 Objectives and Corresponding Endpoints (cont.)

Exploratory Objectives	Corresponding Endpoints
• To characterize the obinutuzumab-induced changes in circulating B cells compared with placebo	• Total peripheral B-cell count via HSFC (MRB 1.1) • Proportion of participants achieving sustained B-cell depletion (<0.441 B-cells/μL of blood at Weeks 24 and 52)
• To evaluate health status utility scores of participants treated with obinutuzumab compared with placebo	• Change from baseline in EQ-5D-5L index-based and VAS scores at Weeks 0, 24, and 52

EQ-5D-5L = EuroQol 5-Dimension, 5-Level Questionnaire; HSFC = high-sensitivity flow cytometry; VAS = Visual Analog Scale.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This is a parallel-group, double-blind, randomized, placebo-controlled study evaluating the efficacy and safety of obinutuzumab versus placebo among participants with active, autoantibody-positive SLE treated with standard-of-care therapy.

The complete eligibility criteria are detailed in Section 5 below. In brief, participants must be 18–75 years of age and have SLE as assessed using the 2019 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) classification criteria at screening (see Appendix 8). Participants must have current autoantibody positivity (anti-nuclear antibody [ANA], anti-dsDNA, and/or anti-Smith [Sm]) and low complement (low C3 and/or low C4 and/or low CH50) at screening. Participants must have a high degree of disease activity, as defined by a Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score of ≥8 excluding points for alopecia, headache, and fever; and ≥1 British Isles Lupus Assessment Group (BILAG) Category A manifestation or ≥2 Category B manifestations. There are additional protocol-specific requirements for specific SLEDAI-2K items for determination of eligibility. Participants must also be receiving one or more standard therapies for SLE at a stable dose at the time of randomization. Key exclusion criteria include severe LN; active, severe CNS lupus; evidence of active infection; and other safety-related exclusions (refer to Section 5.2).

Randomized participants will receive four blinded infusions of obinutuzumab 1000 mg or placebo according to the schedule presented below. Standard SLE therapies will be continued, and a corticosteroid taper is required (refer to Section 6.8.1.4). The primary endpoint, Systemic Lupus Erythematosus Responder Index (SRI)(4), will be assessed at Week 52.

A study schema is provided in Section 1.2 (see Figure 1). The schedules of activities are provided in Section 1.3 (see Table 1, Table 2, and Table 3).

4.1.1 Screening

Consenting participants will enter a screening period of up to 28 days to be evaluated for eligibility. Procedures at screening are listed in the schedule of activities (see Table 1). During screening, the SLE Disease Activity Adjudication Group will review blinded data to ensure the reported data are consistent with active SLE and issue queries to sites as needed (refer to Section 8.1.7).

4.1.2 Blinded Treatment

Upon confirmation of eligibility, participants will be randomized in a 1:1 ratio to receive blinded infusions of obinutuzumab 1000 mg or placebo on Day 1 and at Weeks 2, 24, and 26, as shown in Figure 1.

In order to decrease the risk/severity of IRRs, each infusion will be preceded by the following premedications:

- Methylprednisolone: 80 mg IV and
- Acetaminophen/paracetamol: 650–1000 mg by mouth (PO) or intravenously and
- Diphenhydramine: 50 mg PO or intravenously or equivalent dose of similar agent

All randomized participants will present to the study center on Day 1 for administration of the first dose of blinded treatment (obinutuzumab or placebo); clinical and safety monitoring, including disease activity assessment, physical examination, vital signs, and laboratory and safety assessments; patient-reported outcome (PRO) questionnaires; biomarker sample collection; and pharmacokinetic (PK) assessments. Additional study visits for study treatment administration and for safety and PK assessments will be conducted periodically throughout study treatment in accordance with the schedule of activities (see Table 1).

Through Week 52, standard SLE therapies will be continued at stable doses, and oral corticosteroids (OCS) attempted to be tapered when clinically appropriate, as detailed in Section 6.8.1.4.

Blinded infusions will be discontinued if discontinuation criteria are met (refer to Section 7.1). Participants who discontinue study treatment prior to the end of the blinded treatment (Week 52) will complete all remaining assessments as outlined in the schedule of activities (see 'Early Study Discontinuation' column in Table 1) through Week 52 and will progress to study follow-up (SFU).

Participants who complete the blinded treatment (the Week 52 assessment) may be eligible to receive open-label treatment (OLT) with obinutuzumab (refer to Section 4.1.3). The randomized treatment assignment will not be revealed to participants and investigators as they enter OLT or SFU (except through emergency unblinding; see Section 6.3.2).

Participants who do not receive OLT will enter SFU after the Week 52 visit.

4.1.3 Open Label Treatment

After completion of blinded treatment on Week 52, participants who meet all of the following criteria (as assessed by the investigator) will be eligible to receive OLT:

- Need for additional immunosuppression (for disease activity or risk of flare)
- No unmanageable treatment-emergent adverse events or progressive worsening of disease associated with the blinded treatment regimen
- No early discontinuation of the blinded treatment regimen
- No receipt of rescue therapy (refer to Section 6.8.4)

The investigator will review the above criteria and apply best clinical judgment to determine if a participant is eligible for OLT. Investigators may discuss the appropriateness of OLT directly with the Medical Monitor if needed.

OLT will begin on Week 54. In OLT, obinutuzumab 1000 mg IV will be given at Weeks 54, 56, 78, and *104*. Consistent with the IRR-mitigation measures implemented during the blinded treatment, each obinutuzumab infusion during OLT will be preceded by the following premedications:

- Methylprednisolone: 80 mg IV and
- Acetaminophen/paracetamol: 650–1000 mg PO or intravenously and
- Diphenhydramine: 50 mg PO or intravenously or equivalent dose of similar agent

If the decision is made to provide OLT, participants will present to the study center on Week 54 for administration of the first dose of open-label obinutuzumab; clinical and safety monitoring, including disease activity assessment, physical examination, vital signs, and laboratory and safety assessments; PRO questionnaires; biomarker sample collection; and PK assessments. Additional study visits for obinutuzumab administration and for safety and PK assessments will be conducted in accordance with the OLT schedule of activities (see Table 2).

During OLT, standard SLE therapies may be continued and adjusted at the investigator's discretion.

OLT will be discontinued if discontinuation criteria are met (refer to Section 7.1). Participants who discontinue study treatment prior to the end of the OLT (Week 104) will complete all remaining assessments as outlined in the schedule of activities (see the "Study Discontinuation" column in Table 2) through Week 104 and will subsequently enter SFU.

Participants who received open-label obinutuzumab according to the Schedule of Activities for OLT in earlier versions (1,2, and 3) of the protocol, which involved administration of the last OLT infusion at Week 80, will complete remaining OLT visits according to the same version of the SOA for OLT that was initially followed, and then proceed to SFU. As such, no further open-label obinutuzumab infusions will be administered for any participants who received a dose at Week 80.

4.1.4 Study Follow-Up

SFU will occur after completion of study infusions to monitor safety and disease activity. No obinutuzumab infusions will be provided during SFU. Standard-of-care SLE therapies may be provided at the investigator's discretion.

At least six months of SFU is required for all participants. The first SFU visit will be scheduled approximately six months after the previous study visit:

- For participants who do not enter OLT after blinded treatment (last visit Week 52), the first SFU visit will occur on Week 78
- For participants who receive OLT, the first SFU visit will occur on Week 130

At the SFU visit, the absolute $CD19^+$ B-cell count will be measured. For participants with persistent B-cell depletion, defined as an absolute $CD19^+$ B-cell count below the lowest pretreatment value and less than the lower limit of normal (LLN)and who have not received an additional therapy associated with reductions in peripheral B cells, SFU will continue every 6 months until any of the following occurs:

- Return of peripheral $CD19^+$ B cells to the lowest pretreatment value or the LLN, whichever is lower
- Receipt of an additional therapy associated with reductions in peripheral B cells (e.g., belimumab, rituximab, or cyclophosphamide, or use of obinutuzumab outside the study protocol)
- The study ends as outlined in Section 4.4.

4.1.5 Study Completion

Participants will complete the study when any of the following occurs:

- Study follow-up requirements have been completed (see Section 4.1.4).
- The Week 52 visit of blinded treatment has been completed and the investigator intends to treat the participant with obinutuzumab outside the study protocol (e.g., through the Sponsor's continued access provision) without completing the required study follow-up described in Section 4.1.4.
- The study ends as outlined in Section 4.4.

Upon completion of the study, the Sponsor will offer continued access to Roche IMP (obinutuzumab) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Products (see Section 6.6).

4.1.6 Independent Data Monitoring

An independent Data Monitoring Committee (iDMC) will be used to monitor study data on an ongoing basis. The iDMC will meet approximately every three to six months to evaluate unblinded study data, which will be prepared for the committee by an independent Data Coordinating Center (iDCC).

In addition to the regularly scheduled safety reviews, an unscheduled review of the data may be performed at the request of the iDMC or Study Team, on the basis of a perceived concern for participant safety.

The Sponsor's study team will have no direct contact with the iDMC during the trial conduct except for the scheduled open sessions of the iDMC. The iDMC will provide recommendations to the Sponsor's Data Review Board (DRB) chair as described in the iDMC charter. On behalf of the Sponsor, the DRB chair will accept or reject the recommendations.

Further details can be found in the iDMC Charter.

4.1.7 Patient Input into Study Design

Representatives from different organizations within the patient community were interviewed and asked to provide feedback on the following aspects of the study:

- Study design, endpoints, inclusion and exclusion criteria activities, and PROs
- Recruitment and retention (e.g., inclusivity of underserved patient communities, potential recruitment challenges, possible retention challenges)

This feedback was taken into consideration when developing the protocol.

4.2 RATIONALE FOR STUDY DESIGN

4.2.1 Rationale for Study Population

In this study, participants are required to have SLE with one or more detectable autoantibodies, high disease activity, and hypocomplementemia despite treatment with one or more standard therapies. This patient population is at increased risk for major organ involvement, death, and/or complications of treatment, and therefore is appropriate for study in the proposed clinical trial. Hypocomplementemia in particular is associated with worse survival (Nuntana et al. 2006) and increased damage accrual (Nossent et al. 2010). A higher SLEDAI-2K score is associated with increased mortality and damage accrual (Cook et al. 2000; Gladman et al. 2002; Nossent et al. 2010). BILAG disease activity and immunosuppressant use is associated with increased mortality (Lopez et al. 2012).

In addition, this patient population appears to receive the greatest benefit from B-cell targeted therapies, as evidenced by recent clinical trials of therapies targeting B-cell survival factors. With belimumab, in a post-hoc analysis from pooled data from two pivotal trials (van Vollenhoven et al. 2012), and a prespecified analysis from a subsequent pivotal trial (Stohl et al. 2017), the greatest degree of clinical benefit on disease activity, risk of subsequent flare, and patient-reported outcomes (PROs) over standard of care alone was observed among patients with high baseline disease activity and those with serologic activity, as evidenced by the presence of anti-dsDNA antibodies and/or hypocomplementemia. Similar findings were seen in subgroup analyses from a Phase II study of atacicept for the treatment of SLE (Merrill et al. 2018) and Sponsor analyses of rituximab and fenebrutinib data (unpublished).

For establishing that a sufficient level of disease activity is present for eligibility, SLEDAI-2K points for alopecia, headache, and fever are excluded because of the frequently nonspecific nature of these signs or symptoms, the difficulty in confirming that these features are attributable to active SLE rather than another cause in a global clinical trial, and their contributions to high placebo response rates in previous trials (Mitsikostas et al. 2004; Yun et al. 2007; Zhou and Yang 2009; Kalunian et al. 2018).

4.2.2 Rationale for Control Group

The efficacy and safety of obinutuzumab has not been defined in an active SLE population without severe LN. To permit an unbiased assessment of obinutuzumab in this population, blinded infusions of obinutuzumab or placebo will be administered. All participants will be required to continue standard-of-care treatment with one or more standard SLE therapies, including OCS; antimalarial agents such as hydroxychloroquine; and conventional immunosuppressants such as azathioprine, MMF, mycophenolic acid, and methotrexate.

Corticosteroids will be managed in a manner that permits adequate treatment of participants in both groups but avoids unnecessary use of high-dose steroids. Upon randomization, participants will receive doses of methylprednisolone 80 mg IV prior to blinded infusions of obinutuzumab or placebo. These doses of methylprednisolone given to reduce the risk and severity of IRRs are also anticipated to result in a rapid and meaningful reduction in disease activity for many participants. In addition, if necessary, an OCS burst may be given prior to Week 12 for treatment of any residual disease activity that warrants an intensification of immunosuppressive therapies. Subsequently, investigators are required to attempt tapering of OCS to a target dose of prednisone $\leq$5 mg/day by Week 24, at which point participants will receive two additional doses of methylprednisolone 80 mg IV prior to blinded infusions at Weeks 24 and 26. Subsequently, OCS must be kept to the minimum possible level and changes in OCS dose will not be permitted between Week 40 and Week 52. Use of corticosteroids that meaningfully exceeds the protocol guidance may result in non-response for subsequent efficacy assessments (see Section 9.4.3).

4.2.3 Rationale for Biomarker Assessments

The variability in response to previous B-cell targeting therapies in SLE is not completely understood. This variability may reflect the heterogeneity of this disease as it relates to varying degrees of B-cell involvement among patients, but it may also point to incomplete B-cell depletion. Predictive and pharmacodynamic (PD) biomarkers have the potential to differentiate between these possible explanations, and samples to assess exploratory biomarkers will be collected in this study to improve understanding of variability seen for clinical outcome to obinutuzumab treatment. Predictive biomarker samples will be collected prior to dosing in an effort to identify patients with B-cell driven pathogenesis who are most likely to respond to obinutuzumab. PD biomarker assessment will evaluate the effects of obinutuzumab on B cells and other immune cells,

and may additionally inform PK/PD modeling to support the dose and dose regimen. As these biomarkers may also have prognostic value, their association with disease progression may also be explored.

4.2.4 Rationale for Non-Standard Clinical Outcome Assessments

SLEDAI-2K and BILAG-2004 are SLE-specific indices frequently used to assess global disease activity in SLE clinical trials and will be incorporated into the study's primary endpoint, SRI(4) (Mikdashi and Nived 2015). Cutaneous Lupus Erythematosus Disease Area and Severity (CLASI) is an instrument specific to cutaneous disease activity and damage in SLE patients and will be used to assess skin responses (Albrecht et al. 2005). Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) is a patient-reported instrument designed to assess physical and mental fatigue with acceptable properties in SLE (Kosinski et al. 2013).

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

The proposed dose and dosing regimen for obinutuzumab in participants with SLE in the current study was based on the potency of obinutuzumab relative to rituximab in nonclinical experiments (Mössner et al. 2010), and a review of the efficacy and safety-response relationships observed in the Phase II NOBILITY study in which obinutuzumab 1000 mg was administered as an IV infusion on Day 1 and Weeks 2, 24, and 26. In the NOBILITY study, achievement of sustained peripheral B-cell depletion was associated with increased achievement of CRR (Furie et al. 2020). Strong positive correlations were observed between exposure (assessed as cumulative area under the concentration-time curve [AUC]) and response to treatment. In addition, B-cell depletion appeared to last longer in patients with higher exposure. There were no clear relationships observed between exposure and safety. The dosing regimen used in the NOBILITY study resulted in continued B-cell depletion through Week 52, at which point 94% of obinutuzumab patients were depleted to $\leq$5 cells/μL. By Week 104, the peripheral B cells had repleted in a majority of obinutuzumab patients, and the proportions of patients with CD19 $\leq$ 5 cells/μL were similar in obinutuzumab and placebo groups (16% vs. 12%).

Population Pharmacokinetic Modeling

A population PK model was developed using data from the NOBILITY study, in which the concentration time course of obinutuzumab in LN patients is accurately described by a linear two-compartment model with a time-varying clearance component which decreases with time and is considered likely related to CD20 target reduction and proteinuria improvement over time. The main covariates influencing pharmacokinetics were body weight, baseline serum albumin concentration, and baseline IgG. Graphical and logistical regression analyses were also conducted to explore relationships between obinutuzumab exposure and PD, safety, and efficacy endpoints. Strong positive correlations were observed between exposure (assessed as cumulative AUC) and response to treatment. In addition, B-cell depletion appeared to last longer in patients

with higher exposure. There were no clear relationships observed between exposure and safety.

Open-Label Treatment

The results from the NOBILITY study also led to the hypothesis that additional obinutuzumab infusions after Week 26 may increase the degree and duration of clinical benefit by maintaining B-cell depletion. In the present study, participants may be eligible to receive additional infusions of obinutuzumab after Week 52 through OLT.

Participants Ineligible for Open-Label Treatment

Participants who do not warrant additional immunosuppression; have unmanageable treatment-emergent adverse events and/or progressive worsening of disease with the blinded treatment regimen; prematurely discontinued the blinded treatment regimen; and/or have received rescue therapy will not be eligible for OLT. These participants will instead enter SFU and receive standard-of-care therapies at the investigator's discretion.

Summary

The proposed dosing regimen for participants with SLE in this study is obinutuzumab 1000 mg IV on Day 1 and at Weeks 2, 24, and 26. Participants randomized to placebo will receive placebo infusions on Day 1 and at Weeks 2, 24, and 26. All blinded infusions will be preceded by methylprednisolone 80 mg IV, acetaminophen/paracetamol 650–1000 mg PO or IV, and diphenhydramine 50 mg PO or intravenously (or equivalent dose of a similar agent) to decrease the risk and severity of IRRs.

4.4 END OF STUDY DEFINITION

The end of this study is defined as the date of the scheduled last participant, last visit (LPLV) or when all participants are discontinued from the study, whichever occurs earlier. No further study follow up visits will occur after the following date: 18 months after all participants have completed or discontinued study drug infusions (blinded and open-label).

The end of the study is expected to occur approximately 3 years after the last participant is enrolled. In addition, the Sponsor may decide to terminate the study at any time.

The total length of the study, from screening of the first participant to the end of the study, is expected to be approximately 72 months (6 years).

4.5 DURATION OF PARTICIPATION

The planned duration of study participation for each individual is at least 1.5 years (18 months), which includes 12 months of blinded treatment and 6 additional months of SFU if OLT is not given. Participants who receive OLT will receive an additional *18* months of OLT, for a total duration of study participation of *3* years (3*6* months).

Additional SFU may be required if persistent B-cell depletion is present (refer to Section 4.1.4).

5. STUDY POPULATION

Approximately 300 participants with SLE will be enrolled in this global study at approximately 150 sites.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The Sponsor is committed to addressing barriers to clinical trial participation and advancing inclusive research. This study will make every effort to enroll a patient population that reflects the real-world patients who experience SLE, namely young non-Caucasian women. Ethnic and racial health disparities research, inclusive research tactics, and general mitigations will be developed and made available to support representative patient enrollment in this study.

5.1 INCLUSION CRITERIA

The inclusion criteria are intended to evaluate parameters that will ensure scientific integrity without unnecessarily excluding participants. For some inclusion criteria a race-, ethnicity-, and/or demographic-adjusted reference interval may be provided.

Participants are eligible to be included in the study only if all of the following criteria apply:

- Participants who are capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the Informed Consent Form and in this protocol
- Participants who are age 18–75 years at the time of signing Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Diagnosis of SLE according to the 2019 EULAR/ACR Classification Criteria ≥12 weeks prior to screening (see Appendix 8)
- ANA ≥ 1:80, or anti-dsDNA and/or anti-Sm antibodies above the upper limit of normal (ULN), as determined by the central laboratory at screening
- Low C3 or low C4 or low CH50 complement as determined by the central laboratory at screening

  Low C3 is required in the presence of known genetic deficiency of C4.
- High disease activity at screening, as defined by all of the following:
  - BILAG-2004: Category A disease in ≥1 organ system and/or Category B disease in ≥2 organ systems

Only clinical manifestations and laboratory abnormalities (as evaluated by the central laboratory) that are present at the time of screening will be considered.

- SLEDAI-2K: score ≥8 with additional requirements listed below for determination of eligibility only

  SLEDAI-2K points for alopecia, headache, and fever are excluded.

  Points for arthritis requires ≥3 swollen and tender joints of which ≥1 must be in the hands or wrists.

  Points for rash requires a morphology and distribution characteristic of active cutaneous lupus with a CLASI Total Activity Score ≥2 excluding points for alopecia and mucosal ulcers.

  Points for mucosal ulcers requires BILAG Category A severe mucosal ulceration, defined as: disabling (significantly interfering with oral intake), extensive & deep ulceration; and must have been observed by a physician.

  Points for hematuria and/or pyuria require the presence of SLEDAI-2K proteinuria.

  Only clinical manifestations and laboratory abnormalities (as evaluated by the central laboratory) that are present at the time of screening will be considered.

- Physician's Global Assessment (PGA): score ≥1.0 on a 0 to 3 Visual Analog Scale (VAS)

- High disease activity on Day 1, as defined by all of the following:
  - SLEDAI-2K: score ≥8 with additional requirements listed below for determination of eligibility only

    SLEDAI-2K points for alopecia, headache, and fever are excluded.

    Points for arthritis requires ≥3 tender and swollen joints of which ≥1 must be in the hands or wrists.

    Points for rash requires a morphology and distribution characteristic of active cutaneous lupus with a CLASI Total Activity Score ≥2 excluding points for alopecia and mucosal ulcers.

    Points for mucosal ulcers requires BILAG Category A severe mucosal ulceration, defined as disabling (significantly interfering with oral intake), extensive and deep ulceration; and must have been observed by a physician.

    Points for hematuria and/or pyuria require the presence of SLEDAI-2K proteinuria.

    To determine the Day 1 score for eligibility, SLEDAI-2K clinical manifestations present on Day 1 plus laboratory manifestations present at screening (as evaluated by the central laboratory) will be considered.

- PGA: score ≥1.0 on a 0 to 3 VAS

- Current receipt of ≥1 of the following classes of standard therapies for the treatment of SLE at stable doses: OCS, antimalarials, conventional immunosuppressants
  - If the participant is receiving an OCS such as prednisone:

    The maximum OCS dose is 30 mg/day prednisone (or equivalent) at screening and during screening.

    The OCS dose must be stable for ≥7 days prior to screening and for ≥7 days prior to Day 1. The OCS dose must not be adjusted by > 5 mg/day prednisone (or equivalent) during screening.

    If OCS are the sole standard therapy for SLE, OCS must have been started ≥ 6 weeks prior to screening and the dose must be ≥10 mg/day prednisone (or equivalent) during screening and on Day 1.
  - If the participant is receiving an antimalarial and/or conventional immunosuppressant:

    The medication(s) must have been started ≥12 weeks prior to screening.

    The medication(s) must be at a stable dose for ≥8 weeks prior to and during screening.

    Up to one conventional immunosuppressant from the following list is permitted: azathioprine, MMF, mycophenolic acid, and methotrexate. Methotrexate may be given via oral, subcutaneous, or intramuscular (IM) routes.

- Antimalarial therapy is required unless there is a documented history of intolerance or toxicity. Permitted antimalarial therapies are chloroquine, hydroxychloroquine, and quinacrine.

- For women of childbearing potential: participants who agree to remain abstinent (refrain from heterosexual intercourse) or use contraception, as defined below:

  Women must remain abstinent or use adequate contraceptive method during the treatment period and for 18 months after the final dose of obinutuzumab or placebo. A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

  Examples of adequate contraceptive methods include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices; male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide. A male condom and a female condom should not be used together because of risk of failure due to friction. The reliability of sexual

abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the individual. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

The Medical Monitor may be consulted if there are any questions related to eligibility criteria.

5.2 EXCLUSION CRITERIA

The exclusion criteria are intended to evaluate parameters that will ensure scientific integrity without unnecessarily excluding participants. For some exclusion criteria a race-, ethnicity-, and/or demographic-adjusted reference interval may be provided.

Participants are excluded from the study if any of the following criteria apply:

- Participants who are pregnant or breastfeeding, or intending to become pregnant during the study or within 18 months after the final dose of obinutuzumab or placebo

  Women of childbearing potential must have a negative urine pregnancy test result at screening. If the results at screening are positive, the test results will be confirmed with a serum pregnancy test.

- Presence of significant lupus-associated renal disease and/or renal impairment, defined by any of the following:
  - UPCR $>$3.5 g/g at screening
  - Renal biopsy performed within the 6 months prior to or during screening showing Class III, IV, and/or V LN
  - eGFR $<$30 mL/min/1.73 m^2 (as estimated using the Chronic Kidney Disease Epidemiology Collaboration equation) or the need for dialysis or renal transplantation
  - In the investigator's opinion, the participant has severe LN that is likely to require treatment with protocol-disallowed therapies.

- Active severe or unstable lupus-associated neuropsychiatric disease or where, in the opinion of the investigator, it is likely to require treatment with protocol-disallowed therapies

  Examples of neuropsychiatric SLE manifestations include, but are not limited to: meningitis, retinitis, cerebral vasculitis, myelopathy, demyelination syndromes, acute confusional state, psychosis, acute stroke or stroke syndrome, cranial neuropathy, status epilepticus or seizures, cerebellar ataxia, and mononeuritis multiplex.

- Active overlap syndrome with mixed connective tissue disease or systemic sclerosis within 12 months prior to screening or during screening

- Catastrophic or severe antiphospholipid syndrome within 12 months prior to screening or during screening

  Antiphospholipid syndrome that is not catastrophic or severe and is adequately controlled by anticoagulant therapy for at least 2 months prior to screening is acceptable.

- History of non-SLE inflammatory skin or joint disease within one year of Day 1 that, in the opinion of the investigator, could interfere with assessments of skin or joint manifestations of SLE
- History of any non-SLE disease treated with oral, IV, or IM corticosteroids for more than 14 days in total during the one year prior to Day 1
- Receipt of any of the following excluded therapies:
  - Any B-cell depleting (e.g., anti-CD20, anti-CD19) or anti-plasma cell therapy such as, but not limited to, obinutuzumab, rituximab, ocrelizumab, ofatumumab, or bortezomib less than 9 months prior to screening or during screening

    If anti-CD20 or anti-CD19 therapy has been received between 9 and 12 months prior to screening, the peripheral $CD19^{+}$ B-cell count must be $\geq$25 cells/μL
  - Cyclophosphamide, tacrolimus, ciclosporin, or voclosporin during the 2 months prior to screening or during screening
  - Any biologic therapy (other than anti-CD20, anti-CD19, or anti-plasma cell) such as, but not limited to, belimumab, ustekinumab, anifrolumab, secukinumab, or atacicept during the 2 months prior to screening or during screening
  - Inhibitors of Janus-associated kinase (JAK), Bruton's tyrosine kinase (BTK), or tyrosine kinase 2 (TYK2), including baricitinib, tofacitinib, upadacitinib, filgotinib, ibrutinib, or fenebrutinib or any investigational agent during the 2 months prior to screening or during screening
  - Any live vaccine during the 28 days prior to screening or during screening
- High risk for clinically significant bleeding or any condition requiring plasmapheresis, IV immunoglobulin, or acute blood product transfusions
- Significant or uncontrolled medical disease which, in the investigator's opinion, would preclude patient participation
- HIV infection

  For participants with unknown HIV status, HIV testing will be performed locally at screening if required by local regulations.

- Tuberculosis (TB) infection

  Testing for latent TB will be performed locally at screening if required by local regulations or in accordance with local clinical practice.

  Latent TB after completion of appropriate treatment is not exclusionary.

- Active infection of any kind, excluding fungal infection of the nail beds
- Any major episode of infection that also fulfills any of the following criteria:
  - Requires hospitalization during the 8 weeks prior to screening or during screening
  - Requires treatment with IV antibiotics (or anti-infectives) during the 8 weeks prior to screening or during screening
  - Requires treatment with oral antibiotics (or anti-infectives) during the 2 weeks prior to screening or during screening
  - Antibiotics or anti-infectives given in the absence of a major episode of infection are not exclusionary.
- History of serious recurrent or chronic infection
- History of progressive multifocal leukoencephalopathy (PML)
- History of cancer, including solid tumors, hematological malignancies, and carcinoma in situ, within the past 5 years

  Participants with non-melanomatous carcinomas of the skin that have been treated or excised and have resolved are eligible.
- Major surgery requiring hospitalization during the 4 weeks prior to screening or during screening
- Current alcohol or drug abuse or history of alcohol or drug abuse within 12 months prior to screening or during screening
- Intolerance or contraindication to study therapies, including any of the following:
  - History of severe allergic or anaphylactic reactions to monoclonal antibodies or known hypersensitivity to any component of the obinutuzumab infusion
  - Intolerance or contraindication to oral or IV corticosteroids
  - Lack of peripheral venous access
- Any of the following laboratory parameters:
  - AST or ALT $>2.5\times$ ULN
  - Neutrophils $<1.5\times10^3/\mu L$
  - Positive hepatitis B surface antigen (HBsAg)

    Participants who are HBsAg negative and hepatitis B core antibody (HBcAb) positive with no detectable hepatitis B virus (HBV) DNA are eligible but will require monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo.
  - Positive hepatitis C serology

    Participants with positive hepatitis C antibody test result with no detectable hepatitis C virus (HCV) RNA for at least 6 months after completion of antiviral therapy are eligible but will require monthly HCV RNA monitoring until 12 months after the last dose of obinutuzumab or placebo.

- Hemoglobin < 7 g/dL, unless due to active to SLE
- Platelet count <50,000/μL, unless due to active SLE

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

This study has no meal or dietary restrictions.

5.3.2 Caffeine, Alcohol, and Tobacco

Participants with current alcohol or drug abuse or a history of alcohol or drug abuse within 12 months prior to screening or during screening are excluded from the study (see Section 5.2).

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

During the study, participants must use contraception or take other precautions as described in Section 5.1.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for 3 re-screening opportunities (for a total of 4 screenings per individual) at the investigator's discretion. Individuals are not required to re-sign the Informed Consent Form if they are re-screened within 35 days after previously signing the consent form. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT(S) AND CONCOMITANT THERAPY

Study treatment is defined as any investigational treatment, marketed product, placebo, or medical device intended to be administered to a study participant according to the study protocol.

The IMP for this study is obinutuzumab and placebo.

All premedications and standard-of-care therapies are considered auxiliary medicinal product (AxMP) or non-investigational medicinal products (NIMP).

Appendix 21 identifies all IMP, AxMP, and/or NIMP for this study.

6.1 STUDY TREATMENTS ADMINISTERED

Table 5 provides a description of assigned study treatments for this study.

Table 5 Study Treatment Description

	Obinutuzumab	Placebo	Methylprednisolone	Acetaminophen/ Paracetamol	Diphenhydramine hydrochloride
Use	Experimental	Placebo	Premedication	Premedication	Premedication
Type of medicinal product	IMP	IMP (given solely to preserve the blind; not given as a comparator)	NIMP	NIMP	NIMP
Drug form	Liquid concentrate	Liquid concentrate	Liquid concentrate	Tablet	Tablet
Dosage Level(s)	1000 mg QD	1000 mg QD	80 mg (or 1.5 mg/kg if ≤45 kg)	15 mg/kg (rounded to the nearest available pill formulation, maximum dose 1000 mg)	0.5–1 mg/kg (rounded to the nearest available pill formulation, maximum dose 50 mg)
Formulation(s)	Refer to pharmacy manual and the Obinutuzumab Immunology Investigator's Brochure.	Refer to pharmacy manual.	Refer to local prescribing information.	Refer to local prescribing information.	Refer to local prescribing information.
Packaging	50-mL glass vials	50-mL glass vials	As described in local prescribing information	As described in local prescribing information	As described in local prescribing information
Labeling	Per local requirements				
Route of administration	IV	IV	IV	PO or IV	PO or IV
Source	Sponsor	Sponsor	Site	Site	Site

IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; PO = by mouth; QD = once a day.

The treatment regimens are summarized in Section 4.1.

Guidelines for dose modification and treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 6.

6.1.1 Obinutuzumab

Obinutuzumab will be supplied by the Sponsor as sterile liquid in 50-mL glass vials. For information on the formulation and handling of obinutuzumab, see the Obinutuzumab Immunology Investigator's Brochure and pharmacy manual.

Obinutuzumab must be administered in a hospital or clinic environment where full resuscitation facilities are immediately available and under close supervision of the investigator or designee. Administration of obinutuzumab will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7.

Obinutuzumab 1000 mg will be administered by IV infusion on Day 1 and at Weeks 2, 24, and 26. If OLT is given, infusions will be administered at Weeks 54, 56, 78, and *104*.

Obinutuzumab infusions will be administered per the instructions outlined in Table 6 and additional guidance for study drug administration is found in Appendix 9.

Table 6 Administration of First and Subsequent Infusions of Obinutuzumab

First Infusion	Subsequent Infusions
• Begin infusion at an initial rate of 50 mg/hr. • If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. • If a reaction develops, stop or slow the infusion. Administer medications and give supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	• If the participant experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/hr and follow instructions for first infusion. • If the participant tolerated the prior infusion well (defined by an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hr), begin infusion at a rate of 100 mg/hr. • If no reaction occurs, increase the infusion rate in 100 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. • If a reaction develops, stop or slow the infusion. Administer medications and give supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

Guidelines for medical management of IRRs are provided in the Appendix 6.

If OLT is given, the “first infusion” instructions in Table 6 will be used for the first open-label infusion on Week 54. Subsequent open-label infusions will follow the “subsequent infusions” instructions.

6.1.2 Placebo

Placebo will be supplied by the Sponsor as sterile liquid in 50-mL glass vials. For information on the formulation and handling of placebo, see the Obinutuzumab Immunology Investigator's Brochure and pharmacy manual.

Placebo must be administered in a hospital or clinic environment where full resuscitation facilities are immediately available and under close supervision of the investigator or designee. Administration of placebo will be performed in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions. For anaphylaxis precautions, see Appendix 7.

Placebo (corresponding to the obinutuzumab 1000 mg dose) will be administered as described above in Table 6 for obinutuzumab.

6.1.3 Open-Label Treatment

Participants who receive OLT will be administered open-label obinutuzumab 1000 mg IV on Weeks 54, 56, 78, and *104*. After completion of the final OLT assessment on Week 104, participants will enter SFU (Section 4.1.4).

The randomized treatment assignment will not be unblinded to guide treatment decisions, including whether to provide OLT.

6.1.4 Premedication

All participants who are enrolled in the study will receive premedication prior to administration of obinutuzumab or placebo infusion. For all infusions (blinded or open-label), the following premedications will be administered:

- Methylprednisolone 80 mg IV and
- Acetaminophen/paracetamol 650–1000 mg PO or intravenously and
- Diphenhydramine 50 mg PO or intravenously (or equivalent dose of a similar agent)

The administration of all premedications must be completed between 30 and 60 minutes prior to the obinutuzumab or placebo infusion. OCS should not be given on the day of study drug infusions.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMPs required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMPs supplied by the Sponsor using an interactive voice or web-based response system (IxRS) to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMPs received and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Obinutuzumab Immunology Investigator's Brochure or local prescribing information for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT AND BLINDING

6.3.1 Treatment Assignment

This is a parallel-group, double-blind, placebo-controlled randomized study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a participant, the investigator or the investigator’s research staff will provide participant eligibility information through the IxRS at randomization. Each eligible participant will be

randomized and assigned a unique identification number. As confirmation, the investigator will be provided with written verification of each participant's registration.

Participants will be randomized to receive obinutuzumab or placebo in a 1:1 ratio. The randomization of participants into treatment and control groups will be managed by a central IxRS vendor and will be performed by stratified permutated block design. The stratification factors include screening disease activity and baseline OCS dose as follows:

- Screening disease activity
  SLEDAI-2K score ≥ 12
  SLEDAI-2K score < 12
- Baseline OCS dose
  Prednisone ≥ 10 mg/day
  Prednisone < 10 mg/day

These stratification factors were selected given expected differences in response by baseline disease activity and baseline OCS.

Achievement of SRI(4) requires an absolute reduction of four points or more in the SLEDAI-2K score from baseline, which may represent a small or large relative reduction in a participant's disease activity depending on their baseline total score. Associations have previously been reported between baseline SLEDAI-2K score and the achievement of SRI(4) response (Furie et al. 2014; Gatto et al. 2020). Participants receiving a high dose of corticosteroids at baseline may be at increased risk for flares after protocol-required tapering of dose, in comparison to participants who had a lower or non-existent corticosteroids dose.

6.3.2 Blinding

Study site personnel, investigators, participants, and the Sponsor will be blinded to treatment assignment during the study. Assessment of data collected with the potential to unblind treatment assignment, such as all laboratory studies of blood specimens, will be performed by a central laboratory. Therefore, site personnel and the Sponsor's staff involved with the conduct of the study will not receive unblinded data related to peripheral B-cell counts, PK results, specific immunoglobulin levels (IgM, IgA), or anti-drug antibody (ADA) results until the primary efficacy and safety analyses through Week 52 have been completed.

While PK and immunogenicity samples must be collected from participants assigned to the comparator arm to maintain the blinding of treatment assignment, PK and ADA assay results for these participants are generally not needed for the safe conduct or proper interpretation of the study data. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participant treatment assignments to

identify appropriate samples for analysis. PK samples from participants assigned to the comparator arm will not be analyzed for study drug PK concentration except by request (e.g., to evaluate a possible error in dosing). Baseline immunogenicity samples will be analyzed for all participants. Post-baseline immunogenicity samples from participants assigned to the comparator arm will not be analyzed for ADAs except by request.

If unblinding is necessary for a medical emergency (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. The treatment code should not be broken except in emergency situations. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code. However, the investigator should inform the Medical Monitor that the treatment code has been broken.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 8.3.4) that are considered by the investigator or Sponsor to be related to an IMP (defined in Section 6). The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded on the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.

6.5 DOSE MODIFICATION

Modification of the obinutuzumab dose is not permitted. However, the rate of infusion may be adjusted in the event of an IRR (refer to Section 6.1.1).

If a participant experiences an IRR that requires interruption of the infusion and the investigator determines to permanently discontinue obinutuzumab or placebo infusions, the participant will continue to be followed in the study as outlined in Section 7.1.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to Roche obinutuzumab free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche obinutuzumab after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the participant
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A participant will not be eligible to receive Roche obinutuzumab after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for SLE
- The Sponsor has reasonable safety concerns regarding the IMP as a treatment for SLE
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose of obinutuzumab. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until obinutuzumab can no longer be detected systemically (a minimum of 90 days).

6.8 CONCOMITANT THERAPY

Any medication and/or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements used by a participant in addition to protocol–mandated treatment from 7 days prior to initiation of study treatment to the

completion/discontinuation visit must be recorded on the Concomitant Medications eCRF(s) along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

Under certain circumstances, the Medical Monitor may assess that medications used by a patient more than 7 days prior to screening may need to be captured on the Concomitant Medications eCRF (e.g. COVID-19 vaccinations and latent TB treatment must always be captured on the Concomitant Medications eCRF).

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

Standard SLE therapies, including OCS, antimalarials, conventional immunosuppressants, and premedications are considered NIMPs for this study. Participants must be receiving treatment with ≥1 of these standard SLE therapies at a stable dose to meet eligibility criteria for enrollment.

6.8.1 Corticosteroids

Corticosteroids are permitted during the study within the guidelines described below. All doses are provided in milligrams of prednisone; if necessary, an equivalent dose of an alternative corticosteroid with similar properties to prednisone may be substituted.

It is important that all efforts be made to minimize corticosteroid exposure through Week 52 in order to characterize the effects of obinutuzumab in this patient population.

All participants taking OCS are expected to attempt OCS tapering, when clinically appropriate, in order to reduce their daily dose to a target of ≤5 mg/day prednisone (or equivalent) during the study (refer to Section 6.8.1.4).

From Week 24 onward, corticosteroid use that substantially exceeds the target dosing will result in non-response imputation for subsequent efficacy assessments (refer to Section 6.8.3).

6.8.1.1 Corticosteroid Use Prior to Day 1

At screening, OCS are permitted at a maximum dose of prednisone 30 mg/day (or equivalent). The OCS dose must be stable for ≥7 days prior to screening and ≥7 days prior to Day 1. The OCS dose may not be adjusted by >5 mg/day during screening.

If OCS are given as the sole standard SLE therapy (without antimalarial and conventional immunosuppressants), OCS must have been started ≥6 weeks prior to screening and the dose must be prednisone ≥10 mg/day (or equivalent) at screening and on Day 1.

6.8.1.2 Corticosteroid Premedication

All participants will receive methylprednisolone 80 mg IV as premedication for blinded infusions of obinutuzumab or placebo on Day 1 and Weeks 2, 24, and 26. It is anticipated that these doses of methylprednisolone will result in rapid improvement in SLE disease activity for many participants and no additional corticosteroid burst or increases in daily OCS dose will be necessary.

OCS should not be given on the day of study drug infusions.

6.8.1.3 Corticosteroid Burst

If a participant experiences persistent high disease activity despite infusion premedication with methylprednisolone and requires an acute increase in immunosuppression after Day 1 but prior to Week 12, one of the following corticosteroid bursts may be given:

- New initiation of prednisone ≤30 mg/day (or equivalent), sustained for ≤10 days, then discontinued
- Increase in the dose of existing OCS to a total dose of ≤30 mg/day (or equivalent), sustained for ≤10 days, then returned to the participant's previous OCS dose level
- A single dose of IV or IM methylprednisolone ≤80 mg (or equivalent)
- 1–2 intra-articular/tendon sheath/bursal injections of methylprednisolone for a total dose of ≤80 mg or equivalent

From Week 12 onward, participants are not permitted to receive corticosteroid bursts. If a participant receives a corticosteroid burst or corticosteroid dosage exceeding baseline OCS dose after Week 12, the Medical Monitor must be notified immediately.

6.8.1.4 Corticosteroid Tapering

At each visit prior to Week 40, OCS tapering must be attempted in all participants receiving a dosage of prednisone >5 mg/day when the following clinical tapering criteria are met:

- Clinical stability or improvement compared with the prior visit
- No active SLE manifestations that threaten permanent damage (e.g., renal, CNS, cardiopulmonary, vasculitis, gastrointestinal [GI], active discoid skin lesions) and/or prevent safe reduction in the OCS dose level

The OCS target dosage is prednisone ≤5 mg/day by Week 24 for all participants receiving OCS medication. Tapering attempts for participants taking prednisone >5 mg/day will continue until Week 40 to achieve a substantial reduction in OCS dosage (e.g., ≥25–30%) each month. OCS may be tapered off completely and discontinued if clinically appropriate prior to Week 40. A stepwise dose reduction approach is provided in the corticosteroid taper guidance in Appendix 10.

OCS tapering must start within 14 days of the visit. If OCS tapering is not attempted in an eligible patient, the Medical Monitor must be notified immediately.

OCS dosage level for all participants will be held stable from Week 40 until Week 52, and further tapering or adjustments to OCS dosage are prohibited during this time.

Participants who experience difficulty tolerating OCS tapering prior to Week 40 may temporarily return to the previous OCS dose level or increase prednisone by ≤5 mg/day. The increased OCS dose will be maintained for the minimum amount of time required, and subsequent OCS tapering must be resumed if clinical criteria are met.

Reasons for failing to proceed with the OCS taper must be documented. The Sponsor or its representatives will regularly review clinical and corticosteroid data to ensure tapering is proceeding in eligible participants.

Limited use of corticosteroids for non-SLE conditions (e.g., perioperative management) is permitted prior to Week 40. The non-SLE condition must be documented. Every attempt should be made to minimize the dose and duration of corticosteroids used for non-SLE conditions. From Week 24 onward, use of corticosteroids for non-SLE conditions that exceeds the protocol-specified limits for more than 7 days will result in non-response imputation for subsequent efficacy assessments (refer to Section 6.8.3).

After Week 52, doses of corticosteroids may be adjusted at the discretion of the investigator.

6.8.2 Antimalarials and Conventional Immunosuppressants

If the participant is receiving an antimalarial and/or conventional immunosuppressant, the medication(s) must have been started at least 12 weeks prior to screening and must be at a stable dosage for at least 8 weeks prior to and during screening. Conventional immunosuppressants (azathioprine, MMF, mycophenolic acid, methotrexate) may not be given in combination.

From Day 1 until Week 12, the dosage of existing antimalarial and/or conventional immunosuppressant medication(s) may be increased prior to Week 12 as clinically required. From Week 12 through Week 52, doses of antimalarial and conventional immunosuppressant medication(s) must not be increased. Any increase in the dose level of these therapies after Week 12 will result in non-response imputation for subsequent efficacy assessments.

If intolerance or toxicity occurs, the dosage may be reduced or the medication discontinued. A switch to another agent within the same class of SLE medications due to intolerance or toxicity will be at the investigator's discretion after consulting the Medical Monitor.

New antimalarials or conventional immunosuppressants may not be initiated prior to Week 52. Initiation of new antimalarial or conventional immunosuppressant therapies prior to Week 52 will result in non-response imputation for subsequent efficacy assessments.

After Week 52, doses of antimalarials or conventional immunosuppressants may be adjusted at the discretion of the investigator.

6.8.3 Major Concomitant Therapy Violations

Major concomitant therapy violations will result in non-response imputation for all subsequent efficacy assessments for the primary analysis.

As eligibility for continued study treatment and/or open-label obinutuzumab may be impacted by use of additional immunosuppressive therapy, investigators must notify the Medical Monitor immediately if a participant receives any of the following:

- Corticosteroids*:
  - Week 24 until Week 40:
    - Dosage $>$ 30 mg/day prednisone (or equivalent)
    - Dosage $>$ 5 mg/day prednisone (or equivalent) above the baseline dose
    - New initiation of OCS treatment
    - IV, IM, or intra-articular corticosteroid use (excluding required methylprednisolone 80 mg IV premedication for study drug infusions)

      Exception: $\leq$ 7 days of corticosteroids exceeding these limits are permitted if given for a documented, non-SLE indication (e.g., perioperative management)
  - Week 40 through Week 52:
    - Dosage $>$ 10 mg/day prednisone (or equivalent)
    - Dosage $>$ 5 mg/day prednisone (or equivalent) above the baseline dose
    - Increase in OCS dosage above the Week 40 dose
    - New initiation of OCS treatment
    - IV, IM, or intra-articular corticosteroid use

  *Corticosteroid dose will be calculated as the mean systemic corticosteroid dose via oral, IV, subcutaneous, IM, intra-articular, and intradermal routes over each 7-day period, excluding the required methylprednisolone 80 mg IV premedication given prior to study drug infusions. The baseline dose is calculated using this method during the 7 days prior to Day 1.
- Antimalarials and conventional immunosuppressants:

- At any time: initiation of a new antimalarial or conventional immunosuppressant, except a switch within the same class of SLE medications after consultation with the Medical Monitor (refer to Section 6.8.2)
- From Week 12 onward: increase in the dose of an antimalarial or conventional immunosuppressant

- Rescue medication including cyclophosphamide, rituximab, belimumab, ustekinumab, anifrolumab, baricitinib, and other biologic, targeted, or investigational therapies (see Section 6.8.4)

  Does not include obinutuzumab IMP.
- Plasmapheresis or immunoglobulin therapy
- Other investigational agents

Use of cyclophosphamide, biologic or targeted therapies, plasmapheresis, or other investigational agents will also result in permanent discontinuation of obinutuzumab or placebo infusions, as well as ineligibility for OLT (Section 6.1.3).

6.8.4 Treatment Failure and Rescue Medication

Participants will be considered to have experienced treatment failure in circumstances where severe or organ-threatening disease requires an acute increase in the intensity of therapy beyond protocol-allowed doses and use of rescue medication is recommended by the investigator per SLE treatment guidelines. Rescue medications include the following:

- Cyclophosphamide
- Anti-CD20 antibodies including rituximab, ocrelizumab, ofatumumab, and obinutuzumab (if given outside the study protocol)
- Other biologic, targeted, or investigational therapies used for the treatment of SLE, including belimumab, ustekinumab, anifrolumab, and baricitinib

Participants who receive rescue therapy will be considered non-responders for subsequent efficacy assessments and will have permanent discontinuation of obinutuzumab or placebo infusions (see Section 6.8.3). Participants who receive rescue therapy will be ineligible for OLT (see Section 6.1.3).

6.8.5 Permitted Therapy/Other Permitted Therapy

Use of the following concomitant therapies for SLE is permitted as described below.

- Non-steroidal anti-inflammatory drugs (NSAIDs):

  One NSAID agent used at a stable, approved dosage is permitted during the study.

  New NSAID therapy may not be initiated between Week 40 and Week 52.

  On visit days, the NSAID must not be taken until all clinical assessments are completed.

- Acetaminophen/paracetamol:

  Acetaminophen/paracetamol use at approved dosage is permitted during the study.

  On visit days, acetaminophen/paracetamol must not be taken until all clinical assessments are completed.

  On infusion days, care must be taken to ensure the total dose of acetaminophen/paracetamol, including that given for premedication, does not exceed the approved dose range.

- Topical corticosteroids:

  Use of a single topical corticosteroid agent is permitted during the study.

  Topical corticosteroid use may be decreased or discontinued, but must not be increased above the Day 1 dose level during the study.

- Oral contraceptives with a failure rate $<$1% per year (see Section 5.1)
- Bisphosphonate therapy
- Calcium and/or Vitamin D supplementation
- Anticoagulant or anti-platelet therapy for control of thrombotic risk is permitted if started at least 2 months prior to screening.

  Dual anticoagulant and anti-platelet therapy is prohibited.

- COVID-19 vaccination is permitted and, if administered, should be documented on the eCRF as a concomitant medication.

6.8.6 Cautionary Therapy

6.8.6.1 Immunization during Peripheral B-Cell Depletion

The efficacy and safety of immunization during periods of peripheral B-cell depletion have not been adequately studied. It is recommended that a participant's vaccination record and the need for immunization be carefully evaluated prior to receiving obinutuzumab or placebo. For participants who are likely to require immunization in the foreseeable future, such as participants planning to travel to countries where specific immunization is required or participants requiring a vaccination/booster for their professional activity, any required vaccination/booster must be given at least 28 days prior to randomization. Review of a participant's immunization status or need for the following vaccinations in advance of randomization is recommended: tetanus, diphtheria, influenza, pneumococcus polysaccharide, Varicella, hepatitis B, and measles, mumps, and rubella.

The safety and efficacy of immunization with a live or attenuated live vaccine in B cell-depleted participants are not known. For this reason, the use of live or attenuated vaccines (e.g., measles, mumps, rubella, oral polio vaccine, Bacillus Calmette-Guérin, typhoid, yellow fever, vaccinia, or any other vaccines not yet licensed but belonging to this category) is specifically excluded for 28 days prior to screening through the end of study participation.

Vaccines that do not contain live organisms (e.g., influenza, Pneumovax®, tetanus) are not prohibited; however, vaccines received during peripheral B-cell depletion may be less effective.

6.8.6.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown. However, herbal therapies may be used during the study at the discretion of the investigator.

6.8.7 Prohibited Therapy

Use of the following concomitant therapies is prohibited as described below.

- Immunosuppressive agents not specifically allowed in the study
- Live or attenuated vaccines (see Section 6.8.6.1)

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will complete protocol-defined visits and required SFU. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of study treatment discontinuation and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Any event that meets stopping criteria defined in Section 7.1.1 and in Section A6–2.3).
- Receipt of rescue medication (see Section 6.8.4)

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants who discontinue study treatment prior to Week 52 will complete all remaining assessments during blinded treatment through the Week 52 visit. After Week 52, these participants will complete at least 6 months of SFU (refer to Section 4.1.4).

Participants who discontinue study treatment during OLT will complete all remaining assessments during OLT through the Week 104 visit. After Week 104, these participants will complete at least *12* months of SFU (refer to Section 4.1.4).

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant requests to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.1.1 Liver Chemistry Stopping Criteria

Discontinuation of study treatment is required by the investigator when a study participant meets abnormal liver tests as outlined in Section A3–7.7, or if the investigator believes that it is in the best interest of the participant when abnormal liver chemistries not meeting protocol-specified stopping rules.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

A participant may withdraw from the study at any time at his or her own request, or may be discontinued at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a participant withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the participant specifically requests that the samples be destroyed (as documented in the source documents) or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. If the participant is unable or unwilling to comply with study visits, site personnel should assess reasons the participant is unable or unwilling to return to the clinic, and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up and will be withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Medical history and baseline conditions, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse will be recorded at baseline. Any medication and/or vaccine (including over-the-counter or prescription

medicines, vitamins, and/or herbal supplements) used by the participant within 7 days prior to initiation of study treatment will be recorded at baseline. Demographic data, including age, sex, and self-reported race/ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Participants will be closely monitored for safety throughout the study. Participants should be assessed for toxicity prior to each dose; treatment will be administered only if the clinical assessment and local laboratory test values are acceptable. Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

At applicable sites, certain study assessments may be performed by an MN (mobile nursing) professional at the participant's home or another suitable location, to improve access and convenience for participants participating in the study. The Sponsor will select a health-care company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedules of activities (see Section 1.3) will specify the assessments that may be performed by an MN professional.

8.1 SLE DISEASE ACTIVITY ASSESSMENTS

SLEDAI-2K, BILAG-2004, PGA, CLASI, and tender/swollen joint counts comprise the core SLE clinical disease activity assessments used to evaluate efficacy. Therefore, it is critical that these data are reported consistently and accurately.

Each SLE disease activity assessment requires investigator judgement to determine if the manifestation is present and attributable to SLE. Therefore, these assessments will only be completed by study investigators, or a physician designated by the investigator, who have completed disease assessment training and maintain certification. It is strongly recommended that the same assessor perform all longitudinal disease activity assessments on an individual participant.

All study personnel will receive a protocol-specific SLE Disease Activity Assessments Guide that provides detailed guidance on the use of these instruments in this study, including study-specific clarifications and extensions to ensure consistency and accuracy. These data will be regularly reviewed to ensure quality.

8.1.1 SLEDAI-2K

SLEDAI-2K is a valid, reliable, and sensitive instrument for assessing global disease activity (see Appendix 11). SLEDAI-2K contains 24 lupus-related items/descriptors that are marked as "present," and most likely attributable to SLE or as "absent" in the participant within the past month. Each item has a fixed number of points based on general clinical meaningfulness (range: 1–8), with a maximum possible total score of 105. The SLEDAI-2K is valid for assessment of lupus-related items within the past 10 days and the past 30 days (Touma et al. 2011). For this study, a timeframe of 28 days (4 weeks) will be used.

A key principle for SLEDAI-2K scoring is attribution: SLEDAI-2K items will only be scored if the feature is most likely attributable to active SLE rather than alternative causes or chronic damage alone. By indicating that an item is present, the assessor believes the feature represents an active, inflammatory manifestation of SLE; for example, hematuria due to active lupus nephritis. If any SLEDAI-2K item is marked as "absent" due to an alternative non-SLE explanation (e.g., fever due to infection, thrombocytopenia due to drug cause), this alternative explanation must be documented.

SLEDAI-2K scoring will follow the instrument scoring instructions with protocol-specific clarifications (see Table 7 below). Laboratory-based items will reflect the central laboratory results obtained from the same visit for which SLEDAI-2K is completed (e.g., results from samples collected at the Week 4 visit should be used to complete the Week 4 SLEDAI-2K rather than using Week 2 laboratory results).

Detailed and complete guidance for the use of this instrument, as well as the Eligibility Disease Activity Assessment (SLEDAI-2K with selected items modified for eligibility determination, as detailed in Section 5.1), is provided in the SLE Disease Activity Assessments Guide.

Table 7 Protocol-Specific Clarifications for SLEDAI-2K Items

SLEDAI-2K Item	Protocol-Specific Clarification
Lupus headache	• True lupus headache is very rare. [a] It is considered a severe manifestation of neuropsychiatric lupus and should prompt urgent diagnostic evaluation (e.g., with lumbar puncture, neuroimaging, evaluation by a neurologist) and treatment. • Do not record isolated migraine, tension, or cluster headache.
Arthritis	• Arthritis requires tenderness to palpation plus at least one additional sign of inflammation: swelling, effusion, warmth, or erythema. • Do not record isolated tenderness to palpation.
Hematuria	• Hematuria must be attributed to active lupus nephritis and other causes must be excluded. In the absence of proteinuria, attribution to active nephritis would be very unlikely. • Do not record hematuria associated with menstruation. The urine sample must be repeated after menstruation.
Proteinuria	• Exclude stone, infection, or an alternative cause
Pyuria	• Pyuria must be attributed to active lupus nephritis and other causes must be excluded. In the absence of proteinuria, attribution to active nephritis would be very unlikely. • Do not record pyuria associated with vaginal contamination (presence of any squamous epithelial cells) or infection.
Rash	• Do not record damage (e.g., chronic scarred discoid lesions). • A cutaneous lesion can be scored as “rash” or “vasculitis”, but not both. If cutaneous vasculitis is present and SLEDAI-2K vasculitis is scored, rash can only be scored if there is an additional active, non-vasculitic rash present.
Alopecia	• Must have ongoing hair loss without scarring • Do not record alopecia areata, androgenic alopecia, or chronic (inactive) temporal thinning.
Mucosal ulcers	• In most cases, oral ulcers are painless and are located on the posterior hard palate. These may relapse and remit with SLE disease activity in other domains. [b] • Non-ulcerative lesions of the mouth or nose (including isolated erythema) must not be scored. • Recurrent aphthous stomatitis (“canker sores”) lesions are painful, circular or ovoid, and have an erythematous rim. These must not be scored.
Increased DNA binding	• Anti dsDNA antibody above the upper limit of normal (including indeterminate or equivocal) at the central laboratory
Leukopenia	• Lymphopenia without leukopenia must not be scored.

Table 7 Protocol-Specific Clarifications for SLEDAI-2K Items (cont.)

dsDNA = double stranded DNA; SLEDAI-2K = Systemic Lupus Erythematosus Disease Activity Index 2000.

Note for all laboratory items: If central labs for the current visit cannot be reported due to processing or laboratory error, these labs may be repeated within 14 days of the visit date and may be included in SLEDAI-2K scoring. Labs repeated between visits will also count towards the next visit's SLEDAI-2K assessment if completed within 28 days of the assessment.

[a] Mitsikostas et al. 2004.

[b] Rosenbaum et al. 2019.

8.1.2 BILAG-2004

BILAG-2004 is a global disease activity assessment that considers activity within nine organ systems (see Appendix 12). After referring to the item-specific descriptions in the BILAG-2004 Index Glossary (see Appendix 13) to complete the 97-item BILAG-2004 Index, which records the severity of lupus-specific manifestation(s) and change over time by comparing the most recent 4 weeks of disease activity to that of the previous 4 weeks, each domain is assigned a category grade from A through E to describe the severity of organ involvement (A being the most severe and E being never involved) using the domain-specific algorithms detailed in the BILAG-2004 Index Scoring guidance (see Appendix 14).

At screening only, upon completion of the BILAG-2004 Index, the investigator should assign Category A and/or B grades to applicable domains for eligibility determination. All other visits involving BILAG-2004 assessment only require completion of the BILAG-2004 Index (with the Sponsor responsible for assigning domain-specific category grades upon receipt of data recorded on the BILAG-2004 Index).

Laboratory-based items will reflect the central laboratory results obtained from the same visit at which the BILAG-2004 Index is completed (e.g., results from samples collected at the Week 4 visit should be used to complete the Week 4 BILAG-2004 Index rather than using Week 2 laboratory results).

Detailed guidance for the use of the BILAG-2004 instrument is provided in Appendix 12–Appendix 14 and the SLE Disease Activity Assessments Guide.

In most cases, BILAG Category A and B scores correspond to worsening and/or significant SLE disease activity. However, the BILAG-2004 Index Scoring algorithms give unexpected results when a Category A or B manifestation improves and stabilizes, but remains present to a degree that fulfills the higher-category definition in the BILAG-2004 Index Scoring because it still meets severity criteria described in the BILAG-2004 Index Glossary. These "False A" or "False B" scores occur because only clinical improvement, not stability, results in an improved letter score from prior assessments.

To prevent participants from being assigned worsening scores despite stable disease, a protocol-specific BILAG-2004 scoring rule has been added:

- Manifestations fulfilling "same" criteria after fulfilling "improving" criteria will not result in an increase in the BILAG category grade in the absence of worsening

The Sponsor or its representatives will review blinded BILAG-2004 scoring to ensure the data are consistent and accurate.

8.1.3 PGA

PGA is the physician's assessment of overall SLE disease severity over the past 4 weeks (see Appendix 15). This instrument factors in all aspects of the participant's SLE disease activity, including both clinical and laboratory assessments. It does not reflect non-SLE medical conditions.

The PGA must be completed by a trained and certified investigator. Given the inherent subjectivity in this assessment, the same assessor must evaluate a given participant over time whenever possible.

The PGA is scored from 0 (no SLE activity) to 3 (the most severe SLE activity) on a VAS. Specific guidance on PGA values is given below.

PGA Score	Interpretation
3	The most severe possible SLE activity in any SLE participant, This score is very rare.
> 2.5	Severe SLE activity, This typically warrants urgent treatment with highly active therapies.
2	Moderate SLE activity
1	Mild SLE disease activity
0	No SLE activity

SLE = systemic lupus erythematosus; PGA = Physician's Global Assessment.

When scoring PGA, the score from the previous visit must be reviewed first, and the score for the present visit must be assigned relative to the previous visit's disease activity.

8.1.4 CLASI

CLASI is a validated instrument for assessing cutaneous lupus erythematosus activity (see Appendix 19). It reports two global scores: one for current inflammatory activity (Total Activity Score), and one for damage (Total Damage Score).

To calculate the total scores described above, trained assessors evaluate erythema, scale/hypertrophy, dyspigmentation, and scarring/atrophy/panniculitis at 13 anatomic locations plus additional assessments for mucosal lesions and alopecia.

As described in the SLE Disease Activity Assessments Guide, CLASI scoring must be consistent with corresponding items in SLEDAI-2K (rash, alopecia, mucosal ulcers, vasculitis) and BILAG-2004 scoring.

8.1.5 Joint Counts

A 28-joint count of swollen and tender joints is performed at each visit. The following joints on left and right sides are examined:

- Metacarpophalangeal 1–5
- Proximal interphalangeal 1–5
- Shoulder, elbow, wrist, knee

Each joint is evaluated separately for tenderness (via palpation) and swelling. Joints with intra-articular injection within the preceding 4 weeks must be excluded.

As described in the SLE Disease Activity Assessments Guide, joint counts must be consistent with corresponding items in SLEDAI-2K and BILAG-2004 scoring.

8.1.6 Training and Certification for SLE Disease Activity Assessments

The Sponsor or its representatives will provide comprehensive SLE disease activity assessment training. All assessors must complete this training and pass an examination before assessing or enrolling participants. Certification must be maintained through the duration of participation in the study.

8.1.7 Review of SLE Disease Activity Assessment Data

An SLE Disease Activity Adjudication Group comprised of medically trained individuals and support staff will perform regular review of blinded data. This group will remain blinded until the study's primary analysis is completed and will have access to an independent expert on SLE assessments for consultation. This review will incorporate clinical assessments, laboratory measurements, vital signs, concomitant medications, and other relevant data necessary to evaluate the following questions:

- Are the reported data consistent within each visit?
- Are the reported data consistent between visits?
- Are the reported data consistent with the typical presentation and course of active SLE?
- Are the reported data consistent with the scoring instructions for each instrument?
- Are any discrepancies in the data explained and documented?

The SLE Disease Activity Adjudication Group will communicate inconsistencies and other queries to sites during screening and throughout the study to ensure high-quality, accurate clinical data. When prompted, sites will be responsible for reviewing and, if appropriate, updating the reported data in a timely manner.

Additional training, protocol deviations, or other remediation may be assigned by the SLE Disease Activity Adjudication Group if there are inconsistencies or other problems with data quality.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, GI, genitourinary, and neurologic systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

A brief physical examination will include, at a minimum, assessments of the skin, joints, lungs, cardiovascular system, and CNS. Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Vital Signs

Oral or axillary temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed while the participant is in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

Vital signs will be measured in a seated position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse and respiratory rate.

Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Vital sign measurement may be performed by an MN professional.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS interval. Refer to Appendix 6 for withdrawal criteria and any additional readings that may be necessary.

Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation) should be avoided during the pre–ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG reports. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

8.2.4 Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical laboratory tests to be performed and the schedule of activities (see Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 12 months of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Sample collection may be performed by an MN professional.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

8.2.5 Pregnancy Testing

The schedule for pregnancy testing for enrolled female participants is outlined in Section 1.3 and will be conducted as outlined in Appendix 2.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 2.

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment or from the study (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until 12 months after the final dose of study treatment at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the participant is lost to follow-up (as defined in Section 7.3), or the participant withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements *for expedited* safety reporting to the regulatory authorit*ies (which includes the use of applicable systems, such as EudraVigilance),* Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local

regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Obinutuzumab	Obinutuzumab Immunology Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Pregnancy

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 18 months after the final dose of obinutuzumab.

If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

All pregnancies reported during the study should be followed until pregnancy outcome. The Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events.

8.3.6 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.7 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.8 Adverse Events of Special Interest

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section A3–7.7)
- Suspected transmission of an infectious agent by a study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.
- IRRs; Systemic IRRs only (local IRRs are not considered adverse events of special interest)
- Grade ≥3 infections
- Any hepatitis B reactivation
- PML
- Study drug–related neutropenia
- Study drug–related thrombocytopenia
- GI perforations
- Worsening of preexisting cardiac conditions

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 6.

8.3.9 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants, access to Medical Monitors is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Blood samples of approximately 1 mL will be collected for measurement of serum concentrations of obinutuzumab as specified in the schedule of activities (see Section 1.3).

Samples may be collected at additional timepoints during the study if warranted and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the pharmacokinetics of obinutuzumab. Samples collected for analyses of obinutuzumab serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Genetic analyses will not be performed on these serum samples unless consent for this was included in the Informed Consent Form. Participant confidentiality will be maintained. At visits during which serum samples for the determination of multiple aspects of obinutuzumab will be taken, one sample of sufficient volume can be used.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed to allow for assay development and validation (if needed).

Information on unblinding of personnel responsible for performing PK assays is provided in Section 6.3.

8.5 PHARMACODYNAMICS

Refer to Section 8.7 for information on pharmacodynamic biomarkers.

8.6 GENETICS AND/OR PHARMACOGENOMICS

Refer to Section 8.7 and Appendix 5 for information on genetic biomarkers.

8.7 BIOMARKER ASSESSMENTS

The following biomarker samples will be collected, as applicable, from participants at all sites:

- Blood, plasma, and serum samples for exploratory research on biomarkers and biomarker assay development.

Exploratory biomarker research may include, but will not be limited to, proteins and mRNA (including gene signatures) associated with B cells, B-cell subsets, and B-cell activity. Research may involve extraction of DNA or RNA, analysis of DNA modifications, and analysis of proteins or protein fragments; analysis of mutations, single nucleotide polymorphisms, and other genomic variants that allow genomic profiling of immune repertoire. Mandatory samples will not be analyzed for inherited characteristics.

Biomarker samples collected at participating sites and biomarker samples requiring separate consent are described in Section 8.11.1.3.

Genomic research on the optional Research Biosample Repository (RBR) sample will be aimed at exploring inherited characteristics. NGS methods may include whole genome sequencing (WGS) or whole exome sequencing (WES) of blood samples, but only at participating sites (see Section 8.11.1).

Biomarker samples will be collected according to the schedule outlined in Section 1.3. Biomarker samples will be sent to one or several central laboratories or to the Sponsor or a designee. Instructions for the collection and handling of biomarker samples, including sampling procedures, storage conditions, and shipment instructions, are provided in the laboratory manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 8.11), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law, with the exception of the report from Foundation Medicine. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

8.8 IMMUNOGENICITY ASSESSMENTS

Antibodies to obinutuzumab will be evaluated by the measurement of serum concentration from blood samples of approximately 1 mL that will be collected from all participants according to the schedule of activities. Additionally, serum samples should also be collected at the final visit from participants who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to obinutuzumab and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to obinutuzumab and/or further characterize the immunogenicity of obinutuzumab.

The detection and characterization of antibodies to obinutuzumab will be performed through use of a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for obinutuzumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of the study treatment. Samples may be stored for a maximum of 5 years (or according to local regulations) following the last participant’s last visit for the study at

a facility selected by the Sponsor to enable further analysis of immune responses to obinutuzumab.

8.9 HEALTH ECONOMICS AND/OR MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 CLINICAL OUTCOME ASSESSMENTS

PRO and clinician-reported outcome (ClinRO) instruments will be completed to assess the treatment benefit of obinutuzumab. In addition, PRO instruments will enable the capture of each participant's direct experience with obinutuzumab.

PRO data will be collected through the use of the following instruments in the outlined order:

- FACIT-F Scale
- 36-Item Short Form Survey, Version 2 (SF-36 v2)
- EuroQol 5-Dimension Questionnaire, 5-Level Version (EQ-5D-5L)
- Subject's Global Assessment of Disease Activity (SGA)

ClinRO data will be collected through the use of the following instruments in the outlined order:

- Tender/swollen joint count
- CLASI
- SLEDAI-2K
- BILAG-2004
- PGA

8.10.1 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3). At the clinic, instruments will be administered before the participant receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

PRO instruments, translated into the local language as appropriate, will be provided by the Sponsor in either pre-printed booklets to enable the instruments to be administered in the correct order at each specified timepoint.

During clinic visits, PRO instruments should be administered as outlined below:

- Participants' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for participants to complete the instruments, estimated to be 20 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Participants should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Participants should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

  Site staff should review all completed instruments in pre-printed booklets and should ask the participants to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the participants to complete the item or confirm that the item was intentionally left blank.

ClinRO instruments will be completed at the clinic at specified timepoints during the study (see schedule of activities in Section 1.3). ClinRO instruments will be administered prior to the administration of study treatment. Clinicians must complete the official version of each ClinRO instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.

ClinRO data collected electronically will be transmitted to a centralized database maintained by the electronic device vendor.

8.10.2 Description of Clinical Outcome Assessment Instruments

8.10.2.1 EuroQol 5-Dimension, 5-Level Questionnaire

EQ-5D-5L is a validated self-reported health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman- et al. 2011; Janssen et al. 2013) (see Appendix 20). There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a VAS that measures health state. The EQ-5D-5L is designed to capture the participant's current health status. Published weighting systems allow for creation of a single composite score of the participant's health status. The EQ-5D-5L takes approximately 3 minutes to complete. It will be used in this study for informing pharmacoeconomic evaluations.

8.10.2.2 SGA

The SGA is the participant's overall assessment of his or her current disease activity. It is measured on a 100-mm horizontal VAS (see Appendix 19). The left-hand extreme of the line is described as "none" (symptom-free) and the right-hand extreme as "severe."

8.10.2.3 FACIT-F Scale

The FACIT-F Scale is a patient-completed questionnaire consisting of 13 items that assess fatigue and has been validated in patients with SLE (Kosinski et al. 2013). Instrument scoring yields a range from 0 to 52, with higher scores representing better patient status (less fatigue). This questionnaire should be completed by the patient prior to any procedures being performed at the visit, if possible. The form should then be checked by site staff for completeness. A copy of the questionnaire can be found in Appendix 17.

8.10.2.4 SF-36 v2, Acute

The SF-36 v2, Acute, is a multipurpose, 36-item survey that measures 8 domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health (see Appendix 18). It yields scale scores for each of these 8 health domains, and 2 summary measures of physical and mental health: the Physical Component Summary and Mental Component Summary.

8.11 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

8.11.1 Blood Samples for Whole Genome Sequencing or Whole Exome Sequencing (Participants at Participating Sites)

At participating sites, blood samples will be collected for DNA extraction to enable WGS or WES to identify variants that are predictive of response to study treatment, are associated with progression to a more severe disease state are associated with susceptibility to developing adverse events, can lead to improved adverse event monitoring or investigation, or can increase the knowledge and understanding of disease biology and drug safety.

Research will be aimed at exploring inherited characteristics.

The samples may be sent to one or more laboratories for analysis.

Collection and submission of blood samples for WGS or WES is contingent upon the review and approval of the exploratory research by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for WGS or WES, this section of the protocol (Section 8.11.1) will not be applicable at that site.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Blood samples collected for WGS or WES are to be stored until they are no longer needed or until they are exhausted. However, the storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Refer to Section 8.7 for information on availability of data from biomarker analyses.

8.11.1.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

8.11.1.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 8.11.1.2) will not be applicable at that site.

8.11.1.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to obinutuzumab, SLE and related diseases, or drug safety:

- Blood for DNA sample collected at baseline (Day 1)
- Leftover blood, serum, plasma, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via WGS, WES, or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC–approved Informed Consent Form and applicable laws (e.g., health authority requirements).

8.11.1.4 Confidentiality

RBR samples and associated data will be labeled with a unique participant identification number.

Participant medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate

authorization for use and disclosure of personal health information) signed by the participant, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

8.11.1.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants will be told that they are free to choose not to provide optional RBR samples and may withdraw their consent at any time and for any reason during the storage period.
A separate, specific signature will be required to document a participant's agreement to provide optional RBR samples. Participants who choose not to provide optional RBR samples will not provide a separate signature. The investigator should document whether or not the participant has given consent to provide optional RBR samples and (if applicable) the date(s) of consent, by completing the Sample Informed Consent/Withdrawal eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

8.11.1.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the Sample Informed Consent/Withdrawal eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the

site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

8.11.1.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to an individual's participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary efficacy analysis for this trial will compare obinutuzumab with placebo on the basis of SRI(4) achievement at Week 52 to demonstrate superiority of obinutuzumab over placebo. The following null and alternative hypothesis will be tested at a two-sided α=0.05 significance level:

$$H_0: P_{Obinutuzumb} = P_{Placebo}, \text{ versus } H_a: P_{Obinutuzumb} \neq P_{Placebo}$$

for which $P_{Obinutuzumb}$ and $P_{Placebo}$ refer to proportion of participants who achieve SRI(4) for obinutuzumab and placebo, respectively.

Multiplicity Adjustment

Primary and key secondary endpoints will be tested to compare obinutuzumab with placebo groups for the superiority of obinutuzumab over placebo. Type I error will be controlled for multiplicity using fixed sequence method. The primary and key secondary endpoints will be tested in the order documented in the Statistical Analysis Plan (SAP) at a two-sided α=0.05 significance level, proceeding sequentially from the primary endpoint and testing each endpoint after achieving statistical significance on the previous endpoint.

9.2 SAMPLE SIZE DETERMINATION

The primary efficacy endpoint of this study is the proportion of participants who achieve SRI(4). Based upon previous studies, it is estimated that approximately 35% of SLE participants who are receiving standard therapies will achieve SRI(4) at Week 52, and

that the addition of obinutuzumab to standard therapies will induce an overall SRI(4) rate of 55% at Week 52. On the basis of these assumptions, a total of 300 participants randomized to obinutuzumab and placebo groups in a 1:1 ratio (150 participants in each of the obinutuzumab and placebo groups), stratified by baseline disease activity and OCS dose, will yield over 90% power to detect a 20% treatment effect at the two-sided α=0.05 significance level using a Cochran-Mantel-Haenszel (CMH) test, assuming the same SRI(4) proportions across the strata. In addition, a sample size of 300 will achieve a minimal detectable difference of at least 15% in the key secondary endpoints, assuming placebo response rates up to 35%.

Note: "Enrolled" means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled unless otherwise specified by the protocol.

9.3 ANALYSIS SETS

The following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	• All participants who sign the Informed Consent Form and are randomized.
Randomized	• The randomized set will include all participants who are randomized into the study.
Efficacy evaluable	• The modified intent-to-treat (mITT) set will include all randomized participants who have received any amount of study drug. Participants will be grouped according to randomized (assigned) treatment, rather than treatment received. Participants who received an incorrect therapy will be reported under the treatment arm to which they were randomized. All efficacy analyses will be performed using the mITT set.
Safety evaluable	• The safety-evaluable set will include all randomized participants who receive any amount of study drug. Participants who were randomized but did not receive any part of an infusion of study drug will not be included in the safety population. Participants will be grouped and analyzed according to the treatment they actually received. All safety analyses will be performed using the safety-evaluable set.
PK evaluable	• The PK-evaluable set will include all participants in the mITT set who have received any dose of obinutuzumab given as study drug, have at least one postdose PK sample that is evaluable, and have no major protocol deviations that would impact the PK results. All PK analyses will be performed using the PK-evaluable set.

9.4 STATISTICAL ANALYSES

The SAP will be finalized prior to database snapshot for the primary analysis, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the primary and key secondary endpoints.

9.4.1 General Considerations

Analyses of the primary and secondary efficacy endpoints will be stratified by baseline disease activity and OCS dose, unless otherwise noted. The stratification factors as recorded in IxRS will be used.

In addition to specific analyses that are detailed in the following sections, collected data will be defined as summarized:

- For each participant, the first day of study treatment will be designated Study Day 1. Each assessment will be assigned a study day calculated as follows:
  Date of Assessment − Date of Randomization + 1
- Baseline is defined as the last non-missing value prior to the receipt of study treatment. Typically, baseline will be the pre-dose Day 1 assessment, but may include screening results if the pre-dose Day 1 result is not available or missing.
- Intercurrent events include the following:
  - Major concomitant therapy violation
  - Treatment failure and receiving rescue medication
  - Early study discontinuation due to death, lack of efficacy and adverse event (AE)
  - Treatment discontinuation

  Handling of intercurrent events and missing values will be discussed in the following sections and presented in detail in the SAP.

9.4.2 Primary Endpoint

Definition of Primary Endpoint

The primary efficacy endpoint is the proportion of participants who achieve SRI(4) at Week 52, where SRI(4) is defined as all of the following:

- Reduction from baseline of ≥ 4 points in the SLEDAI-2K
- No new systems or organs affected, as defined by ≥ 1 new BILAG Category A or ≥ 2 new Category B items compared with baseline using BILAG-2004
- No worsening from baseline of ≥ 0.30 points on a 3-point PGA-VAS

Estimands

The primary estimand attributes are as follows:

- Population: participants with active, autoantibody-positive SLE as defined by the inclusion criteria and exclusion criteria

- Primary endpoint (variable): SRI(4) at Week 52
- Treatments:
  - Experimental: obinutuzumab 1000 mg IV infusion on Day 1 and at Weeks 2, 24, and 26
  - Control: placebo
- Intercurrent events

  The following intercurrent events will be handled by composite variable strategy (i.e. considered as non-responder):
  - Major concomitant therapy violation
  - Treatment failure and rescue medication
  - Early study discontinuation due to death, lack of efficacy and AE

  The following intercurrent event will be handled by treatment policy strategy:
  - Treatment discontinuation without other concurrent or subsequent intercurrent events (described above)

    If the other intercurrent events occur concurrently with or after treatment discontinuation, the composite variable strategy will be applied (i.e. considered as non-responder).
- Summary measure: difference in proportion of participants who achieve SRI(4) at Week 52

Main Analytical Approach

The proportion of participants achieving SRI(4) across obinutuzumab and placebo groups will be compared using a CMH test with baseline disease activity (SLEDAI $\geq$12 vs. $<$12) and baseline OCS dose (prednisone $\geq$10 mg/day or equivalent vs. not) as stratification factors.

The hypothesis test will be conducted at a two-sided α=0.05 significance level. SRI(4) is a composite endpoint derived using several sources of information. Any missing or ambiguous data will be queried, and all efforts will be made to resolve data issues prior to the primary analysis snapshot and final database lock.

Missing data will be imputed at a component level of SRI(4) using multiple imputation. The SLEDAI-2K total score will be imputed as a continuous variable. BILAG-2004 will be imputed as a binary variable indicating whether the SRI(4) criterion has been met, i.e., no new systems or organs affected as defined by ≥1 new BILAG Category A or $\geq$2 new Category B items compared with baseline. PGA-VAS score will be imputed as a continuous variable. Additional details on the missing data imputation strategy will be provided in the SAP.

9.4.2.1 Sensitivity Analyses

To assess the impact of the missing data and the robustness of the result from the imputation strategy described above, a sensitivity analysis will be conducted. The details of the sensitivity analysis will be provided in the SAP.

9.4.2.2 Supplementary Analyses

To assess the impact of estimands in the main analytical approach, the intercurrent events mentioned above will be handled using other strategies. The details of the supplementary analyses will be provided in the SAP.

9.4.3 Secondary Endpoints

The secondary endpoints are defined in Section 3 (Table 4).

Estimand attributes and main analytical approaches are outlined below. Details of the analysis will be fully specified in the SAP.

Estimand

The estimand attributes for the binary secondary endpoints are defined as follows:

- Population: participants with SLE
- Endpoint (variable): binary secondary endpoint of interest
- Treatments:
  - Experimental: obinutuzumab 1000 mg IV infusion on Day 1 and at Weeks 2, 24, and 26
  - Control: placebo
- Intercurrent events:

  The following intercurrent events will be handled by composite variable strategy (i.e. considered as non-responder):
  - Major concomitant therapy violation
  - Treatment failure and rescue medication
  - Early study discontinuation due to death, lack of efficacy and AE

  The following intercurrent event will be handled by treatment policy strategy:
  - Treatment discontinuation without other concurrent or subsequent intercurrent events (described above)

    If the other intercurrent events occur concurrently with or after treatment discontinuation, the composite variable strategy will be applied (i.e. considered as non-responder)
- Summary measure: Difference in proportion of participants at a specified visit of interest

Estimand attributes for the continuous secondary endpoints are defined as follows *(unless otherwise specified)*:

- Population: participants with SLE
- Endpoint (variable): change from baseline for the variable of interest
- Treatments:
  - Experimental: obinutuzumab 1000 mg IV infusion at Day 1 and Weeks 2, 24, and 26
  - Control: placebo
- Intercurrent events:

  Data after the first occurrence of the following intercurrent event will be imputed using the worst post-baseline value from the following assessment: the last value available prior to the occurrence of the first intercurrent event and all values available after the occurrence of the intercurrent event. The intercurrent events handled by this method include:
  - Major concomitant therapy violation
  - Treatment failure and rescue medication
  - Early study discontinuation due to death, lack of efficacy and AE

  The following intercurrent event will be handled by treatment policy strategy:
  - Treatment discontinuation without other concurrent or subsequent intercurrent events (described above)

    If any of the other intercurrent events occur after treatment discontinuation, the participant will be imputed using the worst post-baseline value mentioned above.
- Summary measure: difference in adjusted means at a specified visit of interest

Definition and Main Analytical Approach

All the secondary endpoints will be compared between obinutuzumab and placebo groups. The type I error rate will be controlled for the primary and key secondary endpoints.

For binary secondary endpoints, the proportion of participants achieving the endpoint of interest across obinutuzumab and placebo groups will be compared using a CMH test with baseline disease activity (SLEDAI $\geq$12 vs. $<$12) and baseline OCS dose (prednisone $\geq$10 mg/day or equivalent vs. not) as stratification factors. Imputation rules for missing data will follow the same approach described in the SAP.

For continuous secondary endpoints, change from baseline to the specified time point (Week 24 or Week 52) will be analyzed using analysis of covariance (ANCOVA) model. The dependent variable will be the change from baseline at the specified timepoint, and the independent variables in the model will be baseline value and stratification factors. Missing assessments will be imputed following the same approach described in the

SAP. Details on each secondary endpoint are outlined in the following section and in the SAP.

9.4.3.1 Key Secondary Objectives

Proportion of Participants Who Achieve SRI(6) at Week 52

The proportion of participants who achieve SRI(6) at Week 52 will be analyzed using the method described for binary secondary endpoints (Section 9.4.3) SRI(6) is defined as achieving all of the following:

- Reduction from baseline of ≥6 points in the SLEDAI-2K
- No new systems or organs affected, as defined by ≥1 new BILAG Category A or ≥2 new BILAG Category B items compared with baseline using BILAG-2004
- No worsening from baseline of ≥0.30 points on a 3-point PGAVAS

Missing data for SLEDAI-2K, BILAG-2004 and PGA-VAS at Week 52 will be imputed following the same method outlined in Section 9.4.2.

Proportion of Participants entering the study on prednisone ≥10 mg/day (or equivalent) Who Achieve Sustained Corticosteroid Control from Week 40 through Week 52

The proportion of participants who achieve sustained corticosteroid control from Week 40 through Week 52 will be analyzed using the method described for binary secondary endpoints (Section 9.4.3). Sustained oral corticosteroid control is defined as a dose reduction by at least 25% to ≤7.5mg/day at Week 40, which is maintained through Week 52. Sustained corticosteroid control from Week 40 through Week 52 requires all of the following:

- No daily treatment with prednisone > 7.5 mg/day (or equivalent) from Week 40 through Week 52
- No receipt of IV, IM, or intra-articular corticosteroids from Week 40 through Week 52

Time to First BILAG Flare Over 52 Weeks

Time to first BILAG flare over 52 weeks is defined as the occurrence of ≥1 new BILAG Category A or ≥2 new BILAG Category B manifestations from the previous visit.

Time to first SLE flare is defined as the time from randomization to the achievement of SLE flare for the first time. Participants completing the 52-week treatment period who do not experience first SLE flare will be censored at Week 52.

Time to first SLE flare will be summarized using Kaplan-Meier curves. A stratified log-rank test will be used to compare the treatment arms over the 52-week treatment period, adjusting for baseline disease activity and OCS dose.

Proportion of Participants Who Achieve a Sustained SRI(4) Response from Week 40 through Week 52

The proportion of participants who achieve Sustained SRI(4) response from Week 40 through Week 52 will be analyzed using the method described for binary secondary endpoints (Section 9.4.3). Sustained SRI(4) requires:

- Achievement of SRI(4) response from Week 40 through Week 52

Missing data for SLEDAI-2K, BILAG-2004, and PGA-VAS at Week 52 will be imputed using the approach discussed in Section 9.4.2.

Proportion of Participants Who Achieve BICLA at Week 52

The proportion of participants who achieve BICLA at Week 52 will be analyzed using the method described for binary secondary endpoints (Section 9.4.3). BICLA is defined as achievement of all of the following:

- Reduction of all baseline BILAG-2004 Category A items to B/C/D and baseline BILAG-2004 Category B items to C/D
- No new systems or organs affected, as defined by ≥1 new BILAG Category A or ≥2 new BILAG Category B items compared with baseline
- No net increase in SLEDAI-2K from baseline
- No worsening from baseline of ≥0.30 points on a 3-point PGAVAS

Missing data for SLEDAI-2K and PGA-VAS at Week 52 will be imputed using the approach outlined in Section 9.4.2.

Details of analysis for key secondary endpoints will be specified in the SAP.

Similar to the primary endpoint, sensitivity analyses may be conducted for the key secondary endpoints using different imputation methods to assess the robustness of the imputation method). The details of the sensitivity analysis will be provided in the SAP.

9.4.3.2 Supportive Secondary Objectives

Proportion of Participants Who Achieve SRI(4) at Week 24

The proportion of participants who achieve SRI(4) at Week 24 will be analyzed using the method described for binary secondary endpoints (Section 9.4.3). Missing data for SLEDAI-2K, BILAG-2004 and PGA-VAS at Week 24 will be imputed using the same method outlined in Section 9.4.2.

Proportion of Participants Who Achieve Clinical SRI(4) at Week 52

The proportion of participants who achieve clinical SRI(4) at Week 52, where clinical SRI(4) is defined as SRI(4) excluding consideration of laboratory SLEDAI-2K items, will be analyzed using the method described for binary secondary endpoints (Section 9.4.3). Missing data for SLEDAI-2K, BILAG-2004 and PGA-VAS at Week 52 will be imputed using the same method outlined in Section 9.4.2.

Proportion of Participants Who Achieve SRI(4) at Week 52 on Low-Dose Corticosteroids

The proportion of participants who achieve SRI(4) at Week 52 on low-dose corticosteroids, defined as prednisone ≤7.5 mg/day (or equivalent), will be analyzed using the method described for binary secondary endpoints (Section 9.4.3). Missing data for SLEDAI-2K, BILAG-2004 and PGA-VAS at Week 52 will be imputed using the method outlined in Section 9.4.2.

Proportion of Participants Who Achieve Lupus Low Disease Activity State (LLDAS) at Week 52

The proportion of participants who achieve LLDAS at Week 52 will be analyzed using the method described for binary secondary endpoints (Section 9.4.3). LLDAS is defined as achievement of all of the following:

- SLEDAI-2K ≤4
- No SLEDAI-2K activity in major organ systems (renal, CNS, cardiopulmonary, vasculitis, fever) and no hemolytic anemia or GI activity
- PGA-VAS ≤1
- Current prednisone dose ≤7.5 mg/day (or equivalent)

Proportion of Participants Who Achieve Definition of Remission in SLE (DORIS) at Week 52

The proportion of participants who achieve DORIS at Week 52 will be analyzed using the method described for binary secondary endpoints (Section 9.4.3). DORIS is defined as achievement of all of the following:

- Clinical SLEDAI-2K = 0
- PGA-VAS < 0.5
- Current prednisone dose ≤5 mg/day (or equivalent)

Missing data for SLEDAI-2K and PGA-VAS at Week 52 will be imputed using the same method outlined in Section 9.4.2.

Change in FACIT-F Scale from Baseline to Week 24 and from Baseline to Week 52

The change in FACIT-F scale from baseline to Week 24 and from baseline to Week 52 will be analyzed using the method specified for continuous secondary endpoints in Section 9.4.3.

Change in SF-36 v2 Bodily Pain Domain Scale from Baseline to Week 24 and from Baseline to Week 52

The change in bodily pain from baseline to Week 24 and from baseline to Week 52 will be analyzed using the method specified for continuous secondary endpoints in Section 9.4.3.

Change in SF-36 v2 Physical Component Summary Scale from Baseline to Week 24 and from Baseline to Week 52

The change in Physical Component Summary Scale from baseline to Week 24 and from baseline to Week 52 will be analyzed using the method specified for continuous secondary endpoints in Section 9.4.3.

Change in Active Joint Count (Swollen plus Tender) from Baseline to Week 24 and from Baseline to Week 52

The change in active joint count (swollen plus tender) from baseline to Week 24 and from baseline to Week 52 will be analyzed using the method specified for continuous secondary endpoints in Section 9.4.3.

Proportion of Participants who Achieve a ≥50% Reduction in Active Joint Counts (Swollen plus Tender) at Each Study Visit

The proportion of participants who achieve a ≥50% reduction in active joint counts (swollen plus tender) at each study visit, among participants with ≥4 active joints at baseline, will be analyzed using the method described for binary secondary endpoints in Section 9.4.3.

Proportion of Participants who Achieve a ≥50% Reduction in CLASI Total Activity Score at Each Study Visit

The proportion of participants who achieve a ≥50% reduction in CLASI Total Activity Score at each study visit, among participants with CLASI Total Activity Score ≥10 at baseline, will be analyzed using the method described for binary secondary endpoints in Section 9.4.3.

Proportion of Participants Who Achieve Sustained Corticosteroid Control from Week 40 through Week 52

The proportion of participants who achieve sustained corticosteroid control from Week 40 through Week 52 will be analyzed using the method described for binary secondary endpoints in Section 9.4.3. Sustained corticosteroid requires all of the following:

- No treatment with prednisone ≥5 mg/day (or equivalent) from Week 40 through Week 52
- No receipt of intravenous, intramuscular, or intra-articular corticosteroids from Week 40 through Week 52

Cumulative Corticosteroid Use through Week 52

The cumulative corticosteroid use (in equivalent milligrams of prednisone) through Week 52 will be analyzed for each treatment group using *descriptive statistics. Details will be specified in the SAP*.

Annualized Flare Rate through Week 52

The annualized flare rate through Week 52 will be compared between the treatment and placebo group using a negative binomial model. The number of flares over the 52-week blinded treatment period will be the response variable. Treatment arm and the stratification factors will be included as covariates. Follow-up time will be used as an offset variable. The treatment coefficient and the 95% CI will be presented. Details of the analysis method can be found in the SAP.

9.4.3.3 Safety Analyses

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs. Study treatment exposure (such as treatment duration, total dose received, and number of cycles) will be summarized with descriptive statistics. All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to NCI CTCAE, v5.0.

Only treatment-emergent adverse events will be included in safety analyses, unless otherwise specified. Treatment-emergent adverse events will be defined as any newly reported adverse event or any worsening of an existing condition that occurred on or after the first dose of obinutuzumab or placebo infusion from the time of the participant's randomization through the completion of the study or until early discontinuation.

Adverse events with missing onset date will be considered to be treatment emergent. Adverse events with partially missing onset date will also be included as treatment emergent when the month (if it was recorded) and the year occur on or later than the month and year of the study treatment start date.

All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be summarized by system organ class (SOC) and preferred term (PT), and will be presented in order of descending frequency summed across the treatment arms within each SOC and PT. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

9.4.3.4 Other Safety Analyses

The safety analyses will be performed on the safety population as defined in Section 9.3.

Safety data collected in blinded treatment, OLT, and SFU period will be presented separately. Safety data will be summarized by obinutuzumab and placebo groups.

9.4.3.5 Pharmacokinetic Analyses

Serum obinutuzumab concentrations will be summarized (mean, minimum, maximum, SD, and geometric mean) and reported in this study. In addition, non-linear mixed effects modelling will be used to analyze the dose concentration–time data of obinutuzumab. PK data will be used to refine a previously developed population PK model describing obinutuzumab PK following IV administration to LN patients, including the effect of major covariates on the main parameters (e.g., clearance). Derivation of individual measures of exposure such as AUC and maximum observed concentration (C_{max}) will depend on the final model used for the analysis.

The population PK analysis will be preceded by exploratory graphical evaluations of the data and will be used to assess the relationships between obinutuzumab exposure and efficacy, and obinutuzumab exposure and safety. Relevant observed relationships between exposure and safety parameters and exposure and efficacy may be further characterized using different approaches such as logistic regression analyses. Additional PK and PD analyses may be conducted as appropriate. Results of the population PK and exposure-response/PD analyses may be reported separately.

9.4.3.6 Immunogenicity Analyses

The immunogenicity analysis population will consist of all participants with at least one ADA assessment. Participants will be grouped according to treatment received or, if no treatment is received prior to study discontinuation, according to treatment assigned.

The number and proportion of ADA-positive and ADA-negative participants at baseline (baseline prevalence) and after drug administration (post-baseline incidence) will be summarized by study treatment group.

- Participants are considered to be ADA-positive at post-baseline incidence if one of the following definitions apply:

  They are ADA-negative or have missing data at baseline but develop an ADA response following study drug exposure (treatment–induced ADA response)

  Or

  They are ADA-positive at baseline and the titer of one or more post-baseline samples with a titer ≥ 0.60 titer unit greater than the titer of the baseline sample (treatment–enhanced ADA response).

- Participants are considered to be ADA-negative at post-baseline incidence if one of the following definitions apply:

They are ADA-negative or have missing data at baseline and all post-baseline samples are negative

Or,

They are ADA-positive at baseline but do not have any post-baseline samples with a titer $\geq$0.60 titer unit greater than the titer of the baseline sample (treatment unaffected).

9.4.4 Exploratory Endpoints

The exploratory endpoints are defined in Section 3 (see Table 4). The analysis of the exploratory endpoints will be documented in the SAP.

9.4.5 Other Analyses

9.4.5.1 Summaries of Conduct of Study

Enrollment, treatment discontinuation, and early discontinuation from the study will be summarized; reasons for study treatment discontinuation and withdrawal from study will be tabulated; and major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be compiled by treatment arm for the randomized population. A summary of screened participants and reasons for screen failure will be provided.

9.4.5.2 Summaries of Treatment Group Comparability/Demographics and Baseline Characteristics

Summaries by treatment arm according to the randomization for clinically important demographic and baseline characteristics will be provided. The variables will be summarized using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables.

The baseline summary will include the following:

- Age (years)
- Sex
- Weight (kg)
- Race
- Ethnicity
- Region
- Baseline disease activity
- Baseline OCS dose
- SLEDAI-2K
- VAS score
- BILAG-2004

9.5 INTERIM ANALYSES

No interim analyses are planned.

9.6 INDEPENDENT DATA MONITORING COMMITTEE

Refer to Section 4.1.6 for information on the iDMC for this study.

10. REFERENCES

Albrecht J, Taylor L, Berlin JA, et al. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Investig Dermatol 2005;125:889–94.

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus, Ann Rheum Dis 2019;78:1151–59.

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Burness CB, McCormack PL. Belimumab: in systemic lupus erythematosus. Drugs 2011;71:2435–44.

Cook RJ, Gladman DD, Pericak D, et al. Prediction of short term mortality in systemic lupus erythematosus with time dependent measures of disease activity. J Rheumatol 2000;27:1892–5.

Deeks ED. Anifrolumab: first approval. Drugs 2021;81:1795–802.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Furie R, Cascino MD, Garg JP, et al. B-cell depletion and response in a randomized, controlled trial of obinutuzumab for proliferative lupus nephritis [abstract]. Lupus Sci Med 2020;7:O35.

Furie R, Nicholls K, Cheng TT, et al. Efficacy and safety of abatacept in lupus nephritis: a twelve-month, randomized, double-blind study. Arthritis Rheumatol 2014;66:379–89.

Gatto M, Saccon F, Zen M, et al. Early disease and low baseline damage as predictors of response to belimumab in patients with systemic lupus erythematosus in a real-life setting. Arthritis Rheumatol 2020;72:1314–24.

Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29:288–91.

Gomez Mendez LM, Cascino MD, Garg J, et al. Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis. Clin J Am Soc Nephrol 2018;13:1502–9.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727–36.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Kasitanon N, Magder LS, Petri M. Predictors of survival in systemic lupus erythematosus. Medicine 2006;85:147–56

Kim M, Merrill JT, Kalunian K, et al. Evaluating duration of response to treatment in systemic lupus erythematosus clinical trials. Lupus Sci Med 2018;5.

Klein C, Lammens A, Schäfer W, et al. Response to: monoclonal antibodies targeting CD20. MAbs 2013;5:337–8.

Kosinski M, Gajria K, Fernandes AW, et al. Qualitative validation of the FACIT-fatigue scale in systemic lupus erythematosus. Lupus 2013;22:422–30.

Lopez R, Davidson JE, Beeby MD, et al. Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. Rheumatology (Oxford) 2012;51:491–8.

Marinov AD, Wang H, Bastacky SI, et al. The Type II anti-CD20 antibody obinutuzumab (GA101) is more effective than rituximab at depleting B cells and treating disease in a murine lupus model. Arthritis Rheumatol [serial on the Internet]. Dec 2020; [cited: 18 January 2021]. Available from: https://pubmed.ncbi.nlm.nih.gov/33277983

Md Yusof MY, Shaw D, El-Sherbiny YM, et al. Predicting and managing primary and secondary non-response to rituximab using B-cell biomarkers in systemic lupus erythematosus. Ann Rheum Dis 2017;76:1829–36.

Merrill JT, Wallace DJ, Wax S, et al. Efficacy and safety of atacicept in patients with systemic lupus erythematosus: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled, parallel-arm, phase IIb study. Arthritis Rheumatol 2018;70:266–76.

Mikdashi J, Nived O. Measuring disease activity in adults with systemic lupus erythematosus: the challenges of administrative burden and responsiveness to patient concerns in clinical research. Arthritis Res Ther 2015;17:183.

Mitsikostas DD, Sfikakis PP, Goadsby PJ. A meta-analysis for headache in systemic lupus erythematosus: the evidence and the myth. Brain 2004;127:1200–9.

Mössner E, Brünker P, Moser S, et al. Increasing the efficacy of CD20 antibody therapy through the engineering of a new type II anti-CD20 antibody with enhanced direct and immune effector cell-mediated B-cell cytotoxicity. Blood 2010;115:4393–402.

Niederfellner G, Lammens A, Mundigl O, et al. Epitope characterization and crystal structure of GA101 provide insights into the molecular basis for type I/II distinction of CD20 antibodies. Blood 2011;118:358–67.

Nossent J, Kiss E, Rozman B, et al. Disease activity and damage accrual during the early disease course in a multinational inception cohort of patients with systemic lupus erythematosus. Lupus 2010;19:949–56.

Reddy V, Klein C, Isenberg DA, et al. Obinutuzumab induces superior B-cell cytotoxicity to rituximab in rheumatoid arthritis and systemic lupus erythematosus patient samples. Rheumatology 2017;56:1227–37.

Rosenbaum JT, Lim LL, Sibley CH. Ocular, aural, and oral manifestations of lupus. In: Wallace D, Hahn B, editors. Dubois' lupus erythematosus and related syndromes (ninth rdition). Elsevier, 2019;556–65.

Stohl W, Schwarting A, Okada M, et al. Efficacy and safety of subcutaneous belimumab in systemic lupus erythematosus: a fifty-two-week randomized, double-blind, placebo-controlled study. Arthritis Rheumatol 2017;69:1016–27.

Touma Z, Urowitz MB, Ibañez D, et al. SLEDAI-2K 10 days versus SLEDAI-2K 30 days in a longitudinal evaluation. Lupus 2011;20:67–70.

van Vollenhoven RF, Petri MA, Cervera R, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis 2012;71:1343–9.

Yun SJ, Lee J-W, Yoon H-J, et al. Cross-sectional study of hair loss patterns in 122 Korean systemic lupus erythematosus patients: A frequent finding of non-scarring patch alopecia. J Dermatol 2007;34:451–5.

Zhou WJ, Yang CD. The causes and clinical significance of fever in systemic lupus erythematosus: a retrospective study of 487 hospitalised patients. Lupus 2009;18:807–12.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Guideline for Good Clinical Practice
- Applicable laws and regulations

The protocol, Informed Consent Form, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trial Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study to the participant or his or her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Form is revised (through an amendment or an addendum) to communicate information that might affect a participant's willingness to continue in the study, the participant or the participant's legally authorized representative must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant’s legally authorized representative.

A participant who is re-screened is not required to sign another Informed Consent Form if the re-screening occurs within 35 days from the previous Informed Consent Form signature date.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.
A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 150 sites globally will participate to enroll approximately 300 participants. Enrollment will occur through an IxRS.

Central facilities will be used for certain assessments throughout the study (e.g., specified laboratory tests, biomarker and pharmacokinetic analyses), as specified in Section 8 and Appendix 2. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate participant safety throughout the study.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and/or other summaries of clinical study results may be available in health authority databases for public access, as required by local

regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or participants unless required by law (with the exception of the report from Foundation Medicine). The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

A1–7 DATA QUALITY ASSURANCE

All participant data relating to the study will be recorded on printed or electronic CRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the Case Report Form (CRF) or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table 1 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for study treatment administration and/or response evaluation. If a local sample is required, it is important that a sample for central analysis be obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or a response evaluation, the results must be entered on the electronic Case Report Form.

Protocol-specific requirements for inclusion and exclusion of participants are detailed in Section 5.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Central Laboratory Tests
• Hematology: CBC, RBC count, WBC count and differential, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and quantitative platelet count • Chemistry panel (serum): Serum chemistries include AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, albumin, cholesterol, total bilirubin, BUN, uric acid, creatinine, random glucose, lactate dehydrogenase, potassium, sodium, chloride, calcium, phosphorus, CPK, and triglycerides. • HBV serology: HBsAg, HBsAb, and total HBcAb for all individuals; HBV DNA for individuals with negative HBsAg and HBsAb tests and a positive total HBcAb test (For participants who are HBsAg negative and HBcAb positive, perform monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab or placebo) • HCV serology: HCV antibody for all individuals; HCV RNA for individuals with a positive HCV antibody test (For participants with positive HCV antibody test with no detectable HCV RNA at least 6 months after completion of antiviral therapy, perform monthly HCV RNA monitoring until 12 months after the last dose of obinutuzumab or placebo) • Quantitative immunoglobulins: IgA, IgG, and IgM • Antiphospholipid antibodies including anti-cardiolipin and anti-beta-2-glycoprotein • Pregnancy test All women of childbearing potential will have a serum pregnancy test at screening if local urine pregnancy results are positive. Urine pregnancy tests will be performed at specified subsequent visits prior to administration of blinded obinutuzumab/placebo infusions. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. • Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, and blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria) • Flow cytometry: B cell (CD19), T cell (CD3, 4, 8) and NK cells (CD16, CD56) via TBNK assay; • B-cells and subsets (including CD19, CD27, CD38, IgD) by means of HSFC
Local Laboratory Tests
• Urine pregnancy test on study treatment days • HIV serology: HIV-1 antibody/HIV-1/2 antibody/HIV-2 antibody • Tuberculosis: testing for latent tuberculosis

HBcAb = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HSFC = high-sensitivity flow cytometry; NK = natural killer; TBNK = T-, B-, natural killer-cell .

Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Appendix 3
Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

  Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an adverse event or serious adverse event. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an adverse event or serious adverse event if they fulfill the definition of an adverse event or serious adverse event.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

  The condition that leads to the procedure is the adverse event.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

  Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]; see Section A3–3.2); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table 1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table 1 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

CTCAE = Common Terminology Criteria for Adverse Events; NCI = National Cancer Institute.
Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings, including histopathology.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of receipt of the information. New or updated information should be recorded on the originally completed Adverse Event eCRF. For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results

- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 12 months after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 12 months after the final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 12 months after the final dose of study treatment), if the event is believed to be related to prior exposure to study treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations. Only one adverse event term should be recorded in the event field of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 INFUSION-RELATED/INJECTION REACTIONS

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study drug infusion should be captured as a diagnosis (e.g., infusion-related reaction) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a participant experiences both a local and systemic reaction to a single administration of study treatment, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

A3–7.2 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

A3–7.3 ADVERSE EVENTS THAT ARE SECONDARY TO OTHER EVENTS

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A3–7.4 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately

(i.e., no more than 24 hours after the investigator becomes aware that the event became serious; see Section A3–5, for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.5 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., ALP and bilirubin 5 × upper limit of normal (ULN) associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.6 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (e.g., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section A3–7.4 for details on recording persistent adverse events).

A3–7.7 ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section A3–7.2)

and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.8 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). This includes death attributed to progression of SLE.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed solely to progression “systemic lupus erythematosus progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.9 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

A3–7.10 LACK OF EFFICACY OR WORSENING OF SYSTEMIC LUPUS ERYTHEMATOSUS

Deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature (i.e., deterioration beyond the expected pattern of progression of the underlying disease) should be recorded as an adverse

event. When recording an unanticipated worsening of SLE activity on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of SLE"). Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

A3–7.11 HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section A3–2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant has not experienced an adverse event
  - Hospitalization due solely to progression of SLE

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours

A3–7.12 CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). For obinutuzumab/placebo, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with obinutuzumab/placebo, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the obinutuzumab and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the obinutuzumab and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the obinutuzumab and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

Appendix 4
Collection of Pregnancy Information

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A4–1 PREGNANCIES IN FEMALE PARTICIPANTS

Female participants of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 18 months after the final dose of obinutuzumab or placebo. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the pregnancy), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event electronic Case Report Form (eCRF). The investigator should discontinue study treatment and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly or birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

Additionally, attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

A4–2 ABORTIONS

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

A4–3 ABNORMAL PREGNANCY OUTCOMES

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomaly, birth defect, ectopic pregnancy) in a female participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event; see Section A3–5).

Appendix 5
Genetics: Use and Analysis of DNA

Genetic variation may impact a participant's response to study treatment and susceptibility to, and severity and progression of, disease. Variable response to study treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and the Institutional Review Board or Ethics Committee allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to obinutuzumab, systemic lupus erythematosus (SLE), and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to obinutuzumab and SLE. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.

DNA samples may be analyzed for Fc-gamma polymorphisms. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to obinutuzumab or study treatments of this class to understand the study disease or related conditions.

The results of genetic analyses may be reported in the Clinical Study Report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on obinutuzumab and treatments of this drug class or SLE continues but no longer than 5 years or other period as per local requirements.

Appendix 6
Safety Plan: Management of Identified and Potential Risks

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Obinutuzumab is currently approved in chronic lymphocytic leukemia (CLL) and follicular lymphoma (FL) and clinical development is ongoing in other malignancies such as non-Hodgkin lymphoma (NHL) as well as autoimmune diseases. The safety plan for participants in this study is based on clinical experience with obinutuzumab in completed and ongoing studies. The anticipated important safety risks for obinutuzumab are outlined below. Please refer to the Obinutuzumab Immunology Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of study participants. Eligibility criteria have been designed to exclude individuals at higher risk for toxicities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

A6–1 RISKS ASSOCIATED WITH OBINUTUZUMAB

A6–1.1 INFUSION-RELATED REACTIONS

The most frequently observed adverse drug reactions in participants who received obinutuzumab during clinical studies in CLL and NHL were infusion-related reactions IRRs), which occurred predominantly during infusion of the first 1000 mg. In participants who received the combined measures for prevention of IRRs at first infusion (glucocorticoid, oral analgesic/antihistamine premedication, omission of anti-hypertensive medication in the morning of the first infusion, and, for CLL participants only, the Cycle 1 Day 1 dose administered over 2 days), a decreased incidence of all grade IRRs was observed. The rates of Grades 3 and 4 IRRs (which were based on a relatively small number of participants) were similar before and after mitigation measures were implemented. The incidence and severity of infusion-related symptoms decreased substantially after the first 1000 mg was infused, with most participants having no IRRs during subsequent administrations of obinutuzumab.

In the majority of participants, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g., anaphylaxis).

In studies where participants received either obinutuzumab or rituximab (another anti-CD20 monoclonal antibody), obinutuzumab-treated participants appeared to have more IRRs compared with participants receiving rituximab in participants being treated for hematologic malignancies.

In the NOBILITY study in participants with lupus nephritis (LN), 10 participants (15.6%) in the obinutuzumab plus mycophenolate mofetil (MMF) arm experienced IRRs (vs. 6 participants [9.8%] in the placebo plus MMF arm) from baseline until Week 104. All IRRs in the obinutuzumab arm were non-serious and except for one Grade 3 IRR were all of Grade 1 or 2. Of the 10 participants, the IRRs occurred at the first infusion in 8 participants; all IRRs resolved and none led to obinutuzumab discontinuation.

Guidelines for management of participants who develop IRRs are provided in Section A6-2.3.

A6–1.2 INFECTIONS

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported.

Obinutuzumab is more potent in B-cell depletion than is rituximab. It is theoretically possible that there is an increased risk of infections with obinutuzumab compared with rituximab. Study BO21004/CLL11 provides the most meaningful assessment of the possible greater risk of infection (Goede et al. 2014). In Stage 1a (obinutuzumab + chlorambucil vs. chlorambucil alone) and Stage 2 (obinutuzumab + chlorambucil vs. rituximab + chlorambucil) of Study BO21004 in participants with CLL, the incidence of infections was similar between the treatment arms. However, compared with the obinutuzumab + chlorambucil arm, participants in the chlorambucil arm showed a higher incidence of serious infections and deaths due to infection; the incidence of serious infections and fatal infections was similar in the obinutuzumab + chlorambucil and rituximab + chlorambucil arms. To date, there is no clear evidence of a difference between rituximab and obinutuzumab regarding infections.

In the NOBILITY study in participants with LN, at the Week 104 data cutoff, a higher incidence of all infections (serious and non-serious) was observed with obinutuzumab compared to placebo (75% vs. 62.3%). However, the placebo arm showed higher incidences of Grade ≥ 3 infection (21.3% vs. 6.3%) and serious infections (18% vs. 7.8%) compared to the obinutuzumab arm.

Guidelines for management of participants who develop infections are provided in Section A6-2.3.

A6–1.3 HEPATITIS B REACTIVATION

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies, including obinutuzumab in hematologic malignancies.

No cases of HBV reactivation were observed in the NOBILITY study in LN as of the Week 104 data cutoff.

Guidelines for management of participants who develop HBV reactivation are provided in Section A6-2.3.

A6–1.4 PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

Progressive multifocal leukoencephalopathy (PML) has been reported in participants treated with obinutuzumab. The diagnosis of PML should be considered in any patient that presents with new onset or changes to preexisting neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) may occur.

Evaluation of PML includes but is not limited to consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (cerebrospinal fluid testing for John Cunningham [JC] viral DNA).

Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant immunosuppressive therapy should also be considered.

Participants should be referred to a neurologist for the evaluation and treatment of PML.

Guidelines for management of participants who develop PML are provided in Section A6-2.3.

A6–1.5 IMMUNIZATIONS

The safety of immunization with live or attenuated viral vaccines following obinutuzumab therapy has not been studied. Vaccination with live virus vaccines is prohibited during treatment and until B-cell recovery.

A6–1.6 NEUTROPENIA

Severe and life-threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab for hematologic malignancies.

In NOBILITY study in participants with LN, as of the Week 104 data cut, drug-related neutropenia was seen in three participants (four events) in the in the obinutuzumab + MMF arm and in two participants (two events) in the placebo + MMF arm. Of the four neutropenia events in the obinutuzumab + MMF arm, two were Grade 4, one

was Grade 3, and one was Grade 2. All events resolved, with two Grade 4 events requiring treatment with filgrastim. No events of study drug-related neutropenia led to study or study drug discontinuation.

Guidelines for management of participants who develop neutropenia are provided in Section A6-2.3.

A6–1.7 THROMBOCYTOPENIA

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab for hematologic malignancy. Fatal hemorrhagic events have also been reported during Cycle 1 in participants treated with obinutuzumab for hematologic malignancy.

In the NOBILITY study, as of the Week 104 data cutoff, no events of study drug-related thrombocytopenia were reported.

Guidelines for management of participants who develop thrombocytopenia are provided in Section A6-2.3.

A6–1.8 COAGULATION ABNORMALITIES, INCLUDING DISSEMINATED INTRAVASCULAR COAGULATION

Coagulation abnormalities, including disseminated intravascular coagulation (DIC), have been reported in patients receiving obinutuzumab for treatment of hematologic malignancies. In the majority of cases, the events have involved subclinical (asymptomatic) changes in platelets and laboratory coagulation parameters following the first infusion, with spontaneous resolution usually occurring by Day 8. In some cases, the events were associated with IRRs and/or tumor lysis syndrome. No specific baseline risk factors for DIC have been identified.

In the NOBILITY study, as of the Week 104 data cutoff, no events of coagulation abnormalities, including DIC, had been reported.

A6–1.9 B-CELL DEPLETION AND RECOVERY

B-cell depletion is defined as levels of peripheral CD19+ B cells below the TBNK assay limit of quantitation using conventional flow cytometry. B-cell recovery is defined as peripheral $CD19^+$ count at the patient's pretreatment baseline level or the lower limit of normal (LLN), whichever is lower.

Obinutuzumab in Lupus Nephritis

In the NOBILITY study, 1000 mg infusions of obinutuzumab on Day 1 and at Weeks 2, 24, and 26 resulted in peripheral B-cell depletion (by HSFC) in 79.6% of participants at Week 52; at Week 104, 8.2% of obinutuzumab participants had B cells depleted.

Obinutuzumab Monotherapy: NHL and CLL Participants

In the Phase II part of study BO21003 (relapsed indolent NHL), 87 participants were included in the obinutuzumab arm and 86 in the rituximab arm. The median level of CD19 cells was 0.079×10^9 cells/L at baseline and decreased rapidly to zero by 2.5 hours post-infusion on Day 1 of Cycle 1. At the end of the treatment phase, of the participants with known B-cell status, 80 participants receiving rituximab (95%) and 82 participants receiving obinutuzumab (96%) had B-cell depletion. At 18 months post-treatment, 5 of 8 participants receiving rituximab and 17 of 19 participants receiving obinutuzumab (among those tested) remained B-cell depleted.

The data from participants with NHL in Studies BO21003 and BO20999 were pooled and analyzed for B-cell depletion (a total of 205 participants). In this population from the pooled analysis, 195 of 202 participants (97%) had B-cell depletion at the end of treatment. At 12 months, 10 of 56 participants (18%) with known B-cell status had recovered B cells.

The data from participants with CLL in Studies BO21003 and BO20999 were pooled and analyzed for B-cell depletion (a total of 38 participants). In this CLL population from the pooled analysis, 30 of 35 participants (86%) with available data had B-cell depletion at the end of treatment. Twenty-seven of these participants had at least 6 months of follow-up information (after the last study drug administration), and after 24 months, 19 of 27 participants (70%) had recovered B cells. Of note, there were no B-cell count data on the remaining 30% of participants because they had progressed, died, or were lost to follow-up before this timepoint.

Obinutuzumab in Combination with Chemotherapy: CLL Participants

In the Phase III study BO21004/CLL11, 40 of 44 participants (91%) in the obinutuzumab + chlorambucil arm with available data had B-cell depletion at the end of treatment. Within 24 months after the end of follow-up, 18 of 40 participants (45%) had recovered B cells, including 5 participants who also experienced disease progression at the time of recovery.

A6–1.10 IMMUNOGLOBULIN DEPLETION AND RECOVERY

When obinutuzumab has been used for treatment of hematologic malignancies, immunoglobulin depletion and recovery has varied. In the Phase I study BO20999, for participants with NHL, the levels of IgA, IgG, and IgM immunoglobulins were either low

or normal for the duration of the treatment period. For the participants with CLL, immunoglobulin levels were low during the course of treatment. In Phase II, across indications (aggressive NHL, indolent NHL, and CLL), changes in baseline mean and median levels of IgA, IgG, and IgM were observed during the treatment period, but baseline levels had been achieved by the end of the treatment period.

In Study BO21003, in Phase II, in the obinutuzumab arm, mean and median values for IgA, IgG, and IgM concentrations were all within the standard reference ranges.

In Study BO21000, the serum levels of IgA, IgG, and IgM decreased from baseline to Cycle 4 and follow-up (Day 28), but the median levels remained within the corresponding normal ranges. No differences between treatment populations or dose groups were observed in either treatment arm.

In the NOBILITY study, the proportion of participants with serum immunoglobulins levels below the LLN (LLN is 0.7 g/L, 5.65 g/L, and 0.4 g/L for IgA, IgG, and IgM, respectively) are provided in Table 1 for both treatment arms. The difference in the percentage of participants below LLN appears to be highest for IgM starting to show 3 months after initiation of treatment and being consistently 3- to 4-fold higher with 38% and 11% at Week 104 for the obinutuzumab and placebo arms, respectively.

Guidelines for management of participants who develop hypogammaglobulinemia are provided in Section A6-2.3.

Table 1 Percent (%) of Participants with IgG, IgA, and IgM levels < LLN [a]

	IgG		IgA		IgM	
Visit	Placebo+ MMF n=61	Obi + MMF n=64	Placebo+ MMF n=61	Obi + MMF n=64	Placebo+ MMF n=61	Obi + MMF n=64
Baseline	21.3	20.3	3.3	0	11.4	17.2
Week 12	18.3	23.0	5.0	1.6	13.3	36.1
Week 24	8.6	16.7	5.2	3.3	12.1	45.0
Week 52	1.8	11.5	1.8	3.3	10.5	41.0
Wek 76	8.2	10.5	2.0	7.0	10.2	38.6
Week 104	4.3	8.9	2.2	8.9	10.9	37.5

LLN = lower limit of normal; MMF = mycophenolate mofetil; Obi = obinutuzumab

[a] Below 0.7 g/L, 5.65 g/L, and 0.4 g/L for IgA, IgG, and IgM, respectively.

Source: CSR WA29748

A6–1.11 GASTROINTESTINAL PERFORATION

In the pivotal study in NHL, cases of gastrointestinal (GI) perforation have been reported in participants treated with obinutuzumab in association with bendamustine. Participants

with NHL may have a tumor involvement of the GI tract (very rare in CLL participants), which may shrink rapidly and lead to an opening in the GI wall.

In the NOBILITY study in participants with LN, as of the Week 104 data cutoff, 1 participant (1.6%) in the placebo + MMF arm and 2 participants (3.1%) in the obinutuzumab + MMF arm experienced GI perforation.

Guidelines for management of participants who develop GI perforation are provided in Section A6-2.3.

A6–1.12 WORSENING OF PREEXISTING CARDIAC CONDITIONS

In participants with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have been reported during treatment with obinutuzumab for hematologic malignancies. These events may occur as part of an IRR and can be fatal. Therefore, participants with a history of cardiac disease should be monitored closely. In addition, these participants should be hydrated with caution in order to prevent a potential fluid overload.

In the NOBILITY study in participants with LN, as of the Week 104 data cutoff, 3 participants (4.7%) in the obinutuzumab + MMF arm and 3 participants (4.9%) in the placebo + MMF arm experienced cardiac disorders. The participants in the obinutuzumab + MMF arm experienced cardiac ventricular thrombosis (×2) and myocardial necrosis (in one participant, all Grade 3, non-serious, resolved with treatment), and Grade 1 tachycardia and Grade 1 bradycardia in one participant each.

Guidelines for management of participants who develop worsening of preexisting cardiac conditions are provided in Section A6-2.3.

A6–2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A6–2.1 DOSE MODIFICATIONS

Dose modification is not permitted during this study; however, the rate of infusion may be adjusted in the event of an IRR.

If a patient experiences an IRR that requires interruption of the infusion and the investigator determines to permanently discontinue obinutuzumab or placebo infusions, the patient should continue to be followed in the study for safety.

A6–2.2 TREATMENT INTERRUPTION

Obinutuzumab/placebo may be withheld in participants who experience toxicity considered to be related to study drug. Obinutuzumab/placebo may be withheld for reasons other than toxicity (e.g., surgical procedures) at the investigator's discretion following consultation with the Medical Monitor. The investigator may consult the Medical Monitor to determine the acceptable length of treatment interruption.

A6–2.3 MANAGEMENT GUIDELINES

Guidelines for management of specific adverse events are outlined in Table 2. Additional guidelines are provided in the subsections below.

Table 2 Guidelines for Management of Participants Who Experience Adverse Events

Event	Action to Be Taken
IRR to obinutuzumab infusion	• Participants who have preexisting cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. • Withholding of anti-hypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. • Participants at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication. • Hypersensitivity may be difficult to distinguish from IRRs. If a hypersensitivity reaction is suspected during infusion (e.g., symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion should be stopped and treatment permanently discontinued. • Participants with known IgE-mediated hypersensitivity to obinutuzumab or any component of the obinutuzumab infusion must not be treated. • For additional guidance see Study Drug Administration in Appendix 9 and Anaphylaxis Precautions in Appendix 7.
Infections: General	• No participant will be enrolled with a major active infection or history of chronic or recurring infections (excluding fungal infection of skin and/or nail beds). • For all serious infectious adverse events, CBC with differential, quantitative immunoglobulins and flow cytometry should be measured within 1 week of onset. • Participants who develop an active infection during the study will have obinutuzumab infusions withheld until the event has resolved. • Participants who require vaccination should be vaccinated at least 28 days prior to receiving obinutuzumab. • Vaccination with live vaccine through the end of study participation is contraindicated (see Section 6.8.6.1).

IRR = infusion-related reactions.

Table 2 Guidelines for Management of Participants Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Infections: Hepatitis B Reactivation	• Hepatitis B screening is required prior to initiation of obinutuzumab. • Participants with active or chronic hepatitis B (surface antigen) will be excluded from the study. • Participants who are core antibody positive (HBcAb+) with no detectable DNA will be allowed into the study but require monthly HBV DNA monitoring until 12 months after the last dose of obinutuzumab. • If HBV reactivation is observed: – Obinutuzumab infusions should be permanently discontinued (see Section 7.1). – Antiviral therapy must be started as per EASL 2017 Clinical Practice guidelines or local guidelines. – Referral to a hepatologist is recommended. • Participants will be monitored regularly for transaminases elevation. If transaminases elevation is observed, participants will be promptly referred to a hepatologist for evaluation and treatment.
Suspected PML	• Stop obinutuzumab infusions. • Obtain neurological consult. • In consultation with a neurologist, an MRI scan and lumbar puncture (to assess for CSF JC viral DNA) are recommended. • Notify the Medical Monitor immediately.
Neutropenia	• Participants who experience neutropenia should be closely monitored with regular laboratory tests until resolution. • If treatment is necessary, it should be administered in accordance with local guidelines and administration of granulocyte colony stimulating factors should be considered. • Any signs of concomitant infection should be treated as appropriate. • Grade 3 or 4 neutropenia that does not resolve to Grade $\leq$2 within 8 weeks is a treatment-discontinuation criterion. • Cases of late-onset neutropenia (occurring $\geq$28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported in studies of obinutuzumab in hematologic malignancy.

CSF = cerebrospinal fluid; EASL = European Association for the Study of the Liver; GI = gastrointestinal; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; IRR = infusion-related reaction; IVIg = intravenous immunoglobulin; JC = John Cunningham; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy.

Table 2 Guidelines for Management of Participants Who Experience Adverse Events (cont.)

Event	Action to Be Taken
Thrombocytopenia	• Participants should be closely monitored for thrombocytopenia. • If thrombocytopenia occurs, regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. • Transfusion of blood products (i.e., platelet transfusion) according to institutional practice is at the discretion of the treating physician. • Thrombocytopenia that does not resolve to Grade ≤ 2 within 8 weeks is a treatment-discontinuation criterion. • Use of all concomitant therapies, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, should also be taken into consideration.
Hypogammaglobulinemia	• Ig levels will be monitored throughout the study period. • IVIg should be considered for participants with recurrent/severe infections despite appropriate treatment, with concomitant hypogammaglobulinemia.
GI perforations	• Participants presenting with new-onset abdominal symptoms should be promptly evaluated.
Worsening of preexisting cardiac conditions	• Closely monitor participants with underlying cardiac conditions • Caution to be taken when hydrating participants with underlying cardiac conditions to prevent a potential fluid overload.

GI = gastrointestinal; IVIg = intravenous immunoglobulin.

Appendix 7
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

ANAPHYLAXIS DEFINITION CRITERIA

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled (Sampson et al. 2006):

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
  - Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that participant (minutes to several hours):
  - Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
  - Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
  - Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that participant (minutes to several hours):

  Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medications are needed in the event of a suspected anaphylactic reaction during study treatment administration in a clinical setting:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intramuscular (preferred route), subcutaneous, IV, or endotracheal administration in accordance with institutional guidelines
- Antihistamines

- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment administration, the following procedures should be performed:

1. Stop the study treatment administration, if possible.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by participant status and as directed by the physician in charge.
6. Continue to observe the participant and document observations.

REFERENCES

Sampson HA, Muñoz-Furlong A, Campbell R, et al. Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium, J Allergy Clin Immunol. 2006;117:391–7.

Appendix 8
2019 European League against Rheumatism (EULAR)/ American College of Rheumatology (ACR) Classification Criteria for Systemic Lupus Erythematosus

Entry criterion

Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria

Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Additional criteria items within the same domain will not be counted.
*Note: In an assay with at least 90% specificity against relevant disease controls.

REFERENCES

Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus, Ann Rheum Dis 2019;78:1151–59.

Appendix 9
Study Drug Administration

ADMINISTRATION OF STUDY DRUG

Study drug (obinutuzumab or placebo) should be given as a slow intravenous (IV) infusion. It should not be administered as an IV push or bolus.

Obinutuzumab must be administered in a hospital or clinic environment where full resuscitation facilities are immediately available and under close supervision of the investigator or designee. The guidelines below may be slowed at the discretion of the investigator based on a participant's clinical presentation. Although obinutuzumab may be administered on an outpatient basis, participants may be observed in a hospital at the discretion of the investigator.

Participants will receive premedication with methylprednisolone 80 mg IV, acetaminophen/paracetamol 650–1000 mg by mouth (PO) or intravenously, and diphenhydramine hydrochloride (HCl) 50 mg PO or intravenously or equivalent dose of a similar agent prior to the start of each infusion. The administration of all premedications must be completed between 30 and 60 minutes prior to the obinutuzumab or placebo infusion. Oral corticosteroids should not be given on the day of study drug infusions.

NOTE: Participants should be cautioned not to operate vehicles or hazardous machinery until their response to diphenhydramine (or similar antihistamine) has been determined.

FIRST INFUSION (DAY 1)

Infusions should be made through a dedicated line and commence at a rate of 50 mg/hr. This may be escalated at a rate of 50 mg/hr every 30 minutes to a maximum of 400 mg/hr. Table 1 presents the schedule for the first infusion.

Table 1 Schedule for First Infusion

Time (min)	Infusion Rate (mg/hr)	Infusion Rate (mL/hr)	Dose in 30 minutes (mg)	Cumulative Dose (mg)
0–30	50	12.5	25	25
31–60	100	25	50	75
61–90	150	37.5	75	150
91–120	200	50	100	250
121–150	250	62.5	125	375
151–180	300	75	150	525
181–210	350	87.5	175	700
212–240	400	100	200	900
241–255 [a]	400	100	200	1000

[a] Should complete infusion at 255 minutes (4 hours, 15 minutes) to complete total dose of 1000 mg.

In the event that the patient experiences an infusion-related reaction (IRR), refer to Table 2 below for infusion rate modification guidelines.

Table 2 Infusion Rate Modification Guidelines for Infusion-Related Reactions

Grade 4 (life-threatening)	• Stop infusion and permanently discontinue therapy.
Grade 3 (severe)	• Temporarily interrupt infusion and treat symptoms. • Upon resolution of symptoms, resume infusion at no more than 50% of the previous rate (the rate being used at the time that the IRR occurred). • The infusion should be kept at the reduced rate for an additional 30 minutes. • If participant does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Table 1 or Table 3). • If the patient experiences a second occurrence of a Grade 3 IRR, stop infusion and permanently discontinue therapy.
Grade 1–2 (mild and moderate)	• Reduce infusion rate to 50% of the infusion rate that was used at the time of the reaction (e.g., from 100 mg/hr to 50 mg/hr) and treat symptoms. • Upon resolution of symptoms, the infusion should be kept at the reduced rate for an additional 30 minutes. • If participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose (see Table 1 or Table 3).

IRR = infusion-related reaction.

After the end of the first infusion, the IV line should remain in situ for at least 2 hours to be able to administer drugs intravenously if necessary. At the end of the remaining infusions, the IV line should remain in place for at least 30 minutes. If no adverse events occur during this period of time, the IV line may be removed.

SUBSEQUENT INFUSIONS

Participants who tolerated the first infusion of obinutuzumab or placebo may receive the second infusion as detailed in Table 3. Participants who experienced an IRR with the first infusion that is deemed by the investigator to be clinically significant should receive study drug as per the initial infusion schedule, with the starting rate of infusion not exceeding 50% of rate associated with the prior reactions. If the infusion reaction during the first infusion occurred at a rate $>$200 mg/hr, then the second infusion rate should start at 100 mg/hr.

Infusions should be made through a dedicated line and commence at a rate of 100 mg/hr. This may be escalated at a rate of 100 mg/hr every 30 minutes to a maximum of 400 mg/hr. Table 3 presents the schedule for the second and subsequent infusions.

In the event that the participant experiences an IRR, refer to Table 2 above for infusion rate modification guidelines.

Note: These recommendations do not address life-threatening events, including anaphylaxis, for which all appropriate standard measures (including full resuscitation medications and equipment) must be available and should be used as clinically indicated.

Table 3 Schedule for Second and Subsequent Infusions

Time (min)	Infusion Rate (mg/hr)	Infusion Rate (mL/hr)	Dose in 30 minutes (mg)	Cumulative Dose (mg)
0–30	100	25	50	50
31–60	200	50	100	150
61–90	300	75	150	300
91–120	400	100	200	500
121–150	400	100	200	700
151–180	400	100	200	900
181–195 [a]	400	100	200	1000

[a] Should complete infusion at 195 minutes (3 hours, 15 minutes) to complete total dose of 1000 mg.

OPEN-LABEL INFUSIONS

For participants who receive OLT (see Section 6.1.3), the first open-label infusion will be administered on Week 54. Refer to the “first infusion” instructions for this first open-label infusion and “subsequent infusions” instructions for all subsequent infusions during OLT.

Appendix 10
Corticosteroid Taper Guidance

Corticosteroid dose equivalents (Table 1) and dose reductions (Table 2) are suggested guidance and may be recommended at specified study visits, if clinically appropriate. The stepwise tapering of corticosteroids should be performed at the discretion of the investigator.

Table 1 Corticosteroid Equivalence Chart

	Equivalent Dose (mg)
Cortisone acetate	25
Hydrocortisone	20
Deflazacort	7.5
Prednisone	5
Prednisolone	5
Methylprednisolone	4
Meprednisone	4
Dexamethasone	0.75
Betamethasone	0.75
Triamcinolone	4
Beclomethasone	0.75

Note: Cortisol (hydrocortisone) is the standard of comparison for glucocorticoid potency. Hydrocortisone is the name used for pharmaceutical preparations of cortisol.

Table 2 Corticosteroid Tapering Schedule

Study Visit	Dose of Oral Prednisone or Equivalent				
Day 1 [a]	10	20	30	40	50
Week 2 [a]	7.5	15	25	30	40
Week 4	7.5	15	20	25	30
Week 8	7.5	10	15	20	20
Week 12	5	10	10	15	15
Week 16	5	7.5	7.5	10	10
Week 20	5	7.5	7.5	7.5	7.5
Weeks 24–52	5	5	5	5	5

[a] Methylprednisolone 80 mg IV will be administered as premedication for infusions on Day 1 and Weeks 2, 24, and 26, and is expected to support OCS tapering.

Appendix 11
Systemic Lupus Erythematosus Disease Activity Index-2000 (SLEDAI-2K)

(Sample; Not to Be Used to Enter Subject Data)

Study No.: _____ Patient Name: _____ Visit Date: _____ _____ _____
d m yr

(Enter weight in SLEDAI-2K Score column if descriptor is present at the time of the visit or in the preceding 30 days)

Weight	SLEDAI 2K SCORE	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	$\geq$ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	>0.5 gram/24 hours
4	_____	Pyuria	>5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	>38° C. Exclude infectious cause.
1	_____	Thrombocytopenia	<100,000 platelets / x10^9/L, exclude drug causes.
1	_____	Leukopenia	< 3,000 white blood cells / x10^9/L, exclude drug causes.
TOTAL SCORE	_____		

Appendix 12
British Isles Lupus Assessment Group (BILAG)-2004 Index

(Sample; Not to Be Used to Enter Subject Data)

BILAG-2004 INDEX **Date:** **Site:** **Patient No:** **DOB:**

- **Only record manifestations/items due to SLE Disease Activity**
- **Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)**
- **TO BE USED WITH THE GLOSSARY**

Record: **ND** **Not Done**
0 **Not present**
1 **Improving**
2 **Same**
3 **Worse**
4 **New**
Yes/No OR Value (where indicated)
•Y/N Confirm this is due to SLE activity (Yes/No)

CONSTITUTIONAL
1. Pyrexia - documented > 37.5ºC ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

MUCOCUTANEOUS
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

NEUROPSYCHIATRIC
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

MUSCULOSKELETAL
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis (severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): **Serum urea (mmol/l):**
African ancestry: Yes/No **Serum albumin (g/l):**

CARDIORESPIRATORY
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

GASTROINTESTINAL
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

OPHTHALMIC
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

RENAL
78. Systolic blood pressure (mm Hg) value ( ) **Y/N•**
79. Diastolic blood pressure (mm Hg) value ( ) **Y/N•**
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) **Y/N•**
82. Urine albumin-creatinine ratio mg/mmol ( ) **Y/N•**
83. Urine protein-creatinine ratio mg/mmol ( ) **Y/N•**
84. 24 hour urine protein (g) value ( ) **Y/N•**
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) **Y/N•**
87. GFR (calculated) ml/min/1.73 m^2 ( ) **Y/N•**
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

HAEMATOLOGICAL
90. Haemoglobin (g/dl) value ( ) **Y/N•**
91. Total white cell count (x 10^9/l) value ( ) **Y/N•**
92. Neutrophils (x 10^9/l) value ( ) **Y/N•**
93. Lymphocytes (x 10^9/l) value ( ) **Y/N•**
94. Platelets (x 10^9/l) value ( ) **Y/N•**
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

Revision: 1/Sep/2009

Appendix 13
British Isles Lupus Assessment Group (BILAG)-2004
Index Glossary

INSTRUCTIONS

- only record features that are **attributable to SLE disease activity and not due to damage, infection, thrombosis (in absence of inflammatory process) or other conditions**
- assessment refers to manifestations occurring in the **last 4 weeks compared with the previous 4 weeks**
- activity refers to disease process which is reversible while damage refers to permanent process/scarring (irreversible)
- damage due to SLE should be considered as a cause of features that are fixed/persistent (SLICC/ACR damage index uses persistence ≥ 6 months to define damage)
- in some manifestations, it may be difficult to differentiate SLE from other conditions as there may not be any specific test and the decision would then lies with the **physician's judgement on the balance of probabilities**
- ophthalmic manifestations usually need to be assessed by an ophthalmologist and these items would need to be recorded after receiving the response from the ophthalmologist
- guidance for scoring:

(4) NEW

- manifestations are recorded as new when it is a new episode occurring in the last 4 weeks (compared to the previous 4 weeks) that has not improved and this includes new episodes (recurrence) of old manifestations
- new episode occurring in the last 4 weeks but also satisfying the criteria for improvement (below) would be classified as improving instead of new

(3) WORSE

- this refers to manifestations that have deteriorated/worsened significantly in the last 4 weeks compared to the previous 4 weeks, sufficient for consideration of increase in therapy

(2) SAME

- this refers to manifestations that have been present for the last 4 weeks and the previous 4 weeks without significant improvement or deterioration (from the previous 4 weeks)
- this also applies to manifestations that have improved over the last 4 weeks compared to the previous 4 weeks but do not meet the criteria for improvement

(1) IMPROVING

- definition of **improvement**: (a) the amount of improvement is sufficient for **consideration of reduction in therapy** and would not justify escalation in therapy

AND

(b) improvement must be **present currently and for at least 2 weeks** out of the last 4 weeks

OR

manifestation that has **completely resolved and remained absent** over the **whole of last 1 week**

(0) NOT PRESENT

(ND) NOT DONE

- it is important to indicate if a test has not been performed (particularly laboratory investigations) so that this will be recorded as such in the database & not as normal or absent (which is the default)

☐ INDICATE (TICK) IF NOT DUE TO SLE ACTIVITY

- for descriptors that are based on measurements (in renal and haematology systems), it is important to indicate if these are not due to lupus disease activity (for consideration of scoring) as they are usually recorded routinely into a database

CHANGE IN SEVERITY CATEGORY

- there are several items in the index which have been divided into categories of mild and severe (depending on definition). It is essential to record mild and severe items appropriately if the manifestations fulfil both criteria during the last 4 weeks

- if a mild item deteriorated to the extent that it fulfilled the definition of severe category (ie changed into severe category) within the last 4 weeks:
  severe item scored as new (4)
  AND mild item scored as worsening (3)

- if a severe item improved (fulfilling the improvement criteria) to the extent that it no longer fulfilled the definition of severe category (ie changed into mild category) within the last 4 weeks:
  severe item scored as not present (0) if criteria for severe category has not been met over last 4 weeks
  or as improving (1) if criteria for severe category has been met at some point over last 4 weeks

AND

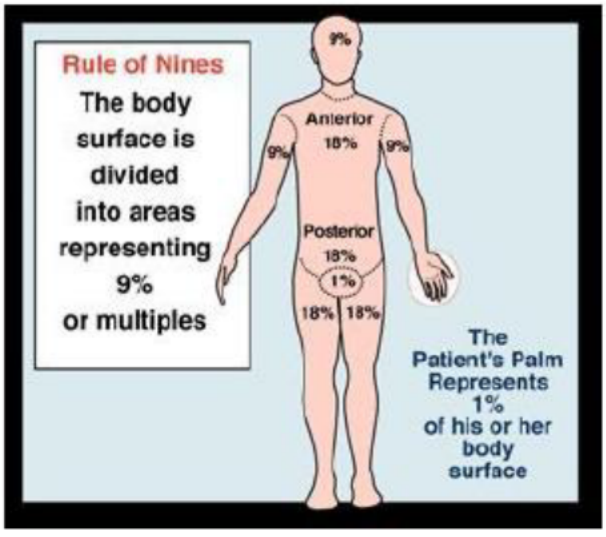
mild item scored as improving (1) if it is improving over last 4 weeks
or as the same (2) if it has remained stable over last 4 weeks

CONSTITUTIONAL

1. Pyrexia	temperature > 37.5°C documented
2. Unintentional weight loss > 5%	
3. Lymphadenopathy	lymph node more than 1 cm diameter exclude infection
4. Anorexia	

MUCOCUTANEOUS

5. Severe eruption	> 18% body surface area any lupus rash except panniculitis, bullous lesion & angio-oedema body surface area (BSA) is estimated using the rules of nines (used to assess extent of burns) as follows: palm(excluding fingers) = 1% BSA each lower limb = 18% BSA each upper limb = 9% BSA torso (front) = 18% BSA torso (back) = 18% BSA head = 9% BSA genital (male) = 1% BSA



6. Mild eruption	≤ 18% body surface area

	any lupus rash except panniculitis, bullous lesion & angio-oedema malar rash must have been observed by a physician and has to be present continuously (persistent) for at least 1 week to be considered significant (to be recorded)
7. Severe angio-oedema	potentially life-threatening eg: stridor angio-oedema is a variant form of urticaria which affects the subcutaneous, submucosal and deep dermal tissues
8. Mild angio-oedema	not life threatening
9. Severe mucosal ulceration	disabling (significantly interfering with oral intake), extensive & deep ulceration must have been observed by a physician
10. Mild mucosal ulceration	localised &/or non-disabling ulceration
11. Severe panniculitis or bullous lupus	any one: > 9% body surface area facial panniculitis panniculitis that is beginning to ulcerate panniculitis that threatens integrity of subcutaneous tissue (beginning to cause surface depression) on > 9% body surface area panniculitis presents as a palpable and tender subcutaneous induration/nodule note that established surface depression and atrophy alone is likely to be due to damage
12. Mild panniculitis or bullous lupus	≤ 9% body surface area does not fulfil any criteria for severe panniculitis (for panniculitis)
13. Major cutaneous vasculitis/thrombosis	resulting in extensive gangrene or ulceration or skin infarction
14. Digital infarct or nodular vasculitis	localised single or multiple infarct(s) over digit(s) or tender erythematous nodule(s)
15. Severe alopecia	clinically detectable (diffuse or patchy) hair loss with scalp inflammation (redness over scalp)

16. Mild alopecia	diffuse or patchy hair loss without scalp inflammation (clinically detectable or by history)
17. Peri-ungual erythema or chilblains	chilblains are localised inflammatory lesions (may ulcerate) which are precipitated by exposure to cold
18. Splinter haemorrhages	
NEUROPSYCHIATRIC	
19. Aseptic meningitis	criteria (all): acute/subacute onset headache fever abnormal CSF (raised protein &/or lymphocyte predominance) but negative cultures preferably photophobia, neck stiffness and meningeal irritation should be present as well but are not essential for diagnosis exclude CNS/meningeal infection, intracranial haemorrhage
20. Cerebral vasculitis	should be present with features of vasculitis in another system supportive imaging &/or biopsy findings
21. Demyelinating syndrome	discrete white matter lesion with associated neurological deficit not recorded elsewhere ideally there should have been at least one previously recorded event supportive imaging required exclude multiple sclerosis
22. Myelopathy	acute onset of rapidly evolving paraparesis or quadriparesis and/or sensory level exclude intramedullary and extramedullary space occupying lesion
23. Acute confusional state	acute disturbance of consciousness or level of arousal with reduced ability to focus, maintain or shift attention

	includes hypo- and hyperaroused states and encompasses the spectrum from delirium to coma
24. Psychosis	delusion or hallucinations does not occur exclusively during course of a delirium exclude drugs, substance abuse, primary psychotic disorder
25. Acute inflammatory demyelinating polyradiculoneuropathy	criteria: progressive polyradiculoneuropathy loss of reflexes symmetrical involvement increased CSF protein without pleocytosis supportive electrophysiology study
26. Mononeuropathy (single/multiplex)	supportive electrophysiology study required
27. Cranial neuropathy	except optic neuropathy which is classified under ophthalmic system
28. Plexopathy	disorder of brachial or lumbosacral plexus resulting in neurological deficit not corresponding to territory of single root or nerve supportive electrophysiology study required
29. Polyneuropathy	acute symmetrical distal sensory and/or motor deficit supportive electrophysiology study required
30. Seizure disorder	independent description of seizure by reliable witness
31. Status epilepticus	a seizure or series of seizures lasting $\geq$ 30 minutes without full recovery to baseline
32. Cerebrovascular disease (not due to vasculitis)	any one with supporting imaging: stroke syndrome transient ischaemic attack intracranial haemorrhage exclude hypoglycaemia, cerebral sinus thrombosis, vascular malformation, tumour, abscess cerebral sinus thrombosis not included as

	definite thrombosis not considered part of lupus activity
33. Cognitive dysfunction	significant deficits in any cognitive functions: simple attention (ability to register & maintain information) complex attention memory (ability to register, recall & recognise information eg learning, recall) visual-spatial processing (ability to analyse, synthesise & manipulate visual-spatial information) language (ability to comprehend, repeat & produce oral/written material eg verbal fluency, naming) reasoning/problem solving (ability to reason & abstract) psychomotor speed executive functions (eg planning, organising, sequencing) in absence of disturbance of consciousness or level of arousal sufficiently severe to interfere with daily activities neuropsychological testing should be done or corroborating history from third party if possible exclude substance abuse
34. Movement disorder	exclude drugs
35. Autonomic disorder	any one: fall in blood pressure to standing > 30/15 mm Hg (systolic/diastolic) increase in heart rate to standing ≥ 30 bpm loss of heart rate variation with respiration (max – min < 15 bpm, expiration:inspiration ratio < 1.2, Valsalva ratio < 1.4) loss of sweating over body and limbs (anhidrosis) by sweat test exclude drugs and diabetes mellitus
36. Cerebellar ataxia	cerebellar ataxia in isolation of other CNS features

	usually subacute presentation
37. Severe lupus headache (unremitting)	disabling headache unresponsive to narcotic analgesia & lasting ≥ 3 days exclude intracranial space occupying lesion and CNS infection
38. Headache from IC hypertension	exclude cerebral sinus thrombosis
MUSCULOSKELETAL	
39. Severe myositis	significantly elevated serum muscle enzymes with significant muscle weakness exclude endocrine causes and drug-induced myopathy electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity
40. Mild myositis	significantly elevated serum muscle enzymes with myalgia but without significant muscle weakness asymptomatic elevated serum muscle enzymes not included exclude endocrine causes and drug-induced myopathy electromyography and muscle biopsy are used for diagnostic purpose and are not required to determine level of activity
41. Severe arthritis	observed active synovitis ≥ 2 joints with marked loss of functional range of movements and significant impairment of activities of daily living, that has been present on several days (cumulatively) over the last 4 weeks
42. Moderate arthritis or Tendonitis or Tenosynovitis	tendonitis/tenosynovitis or active synovitis ≥ 1 joint (observed or through history) with some loss of functional range of movements, that has been present on several days over the last 4 weeks
43. Mild arthritis or Arthralgia or Myalgia	inflammatory type of pain (worse in the morning with stiffness, usually improves with activity & not brought on by activity) over joints/muscle

	inflammatory arthritis which does not fulfil the above criteria for moderate or severe arthritis
CARDIORESPIRATORY	
44. Mild myocarditis	inflammation of myocardium with raised cardiac enzymes &/or ECG changes and without resulting cardiac failure, arrhythmia or valvular dysfunction
45. Cardiac failure	cardiac failure due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) cardiac failure due to myocarditis is defined by left ventricular ejection fraction ≤ 40% & pulmonary oedema or peripheral oedema cardiac failure due to acute valvular regurgitation (from endocarditis) can be associated with normal left ventricular ejection fraction diastolic heart failure is not included
46. Arrhythmia	arrhythmia (except sinus tachycardia) due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) confirmation by electrocardiogram required (history of palpitations alone inadequate)
47. New valvular dysfunction	new cardiac valvular dysfunction due to myocarditis or non-infective inflammation of endocardium or cardiac valves (endocarditis) supportive imaging required
48. Pleurisy/Pericarditis	convincing history &/or physical findings that you would consider treating in absence of cardiac tamponade or pleural effusion with dyspnoea do not score if you are unsure whether or not it is pleurisy/pericarditis
49. Cardiac tamponade	supportive imaging required
50. Pleural effusion with dyspnoea	supportive imaging required
51. Pulmonary haemorrhage/vasculitis	inflammation of pulmonary vasculature with

	haemoptysis &/or dyspnoea &/or pulmonary hypertension supportive imaging &/or histological diagnosis required
52. Interstitial alveolitis/pneumonitis	radiological features of alveolar infiltration not due to infection or haemorrhage required for diagnosis corrected gas transfer Kco reduced to < 70% normal or fall of > 20% if previously abnormal on-going activity would be determined by clinical findings and lung function tests, and repeated imaging may be required in those with deterioration (clinically or lung function tests) or failure to respond to therapy
53. Shrinking lung syndrome	acute reduction (> 20% if previous measurement available) in lung volumes (to < 70% predicted) in the presence of normal corrected gas transfer (Kco) & dysfunctional diaphragmatic movements
54. Aortitis	inflammation of aorta (with or without dissection) with supportive imaging abnormalities accompanied by > 10 mm Hg difference in BP between arms &/or claudication of extremities &/or vascular bruits repeated imaging would be required to determine on-going activity in those with clinical deterioration or failure to respond to therapy
55. Coronary vasculitis	inflammation of coronary vessels with radiographic evidence of non-atheromatous narrowing, obstruction or aneurysmal changes
GASTROINTESTINAL	
56. Lupus peritonitis	serositis presenting as acute abdomen with rebound/guarding
57. Serositis	not presenting as acute abdomen
58. Lupus enteritis or colitis	vasculitis or inflammation of small or large bowel with supportive imaging &/or biopsy findings
59. Malabsorption	diarrhoea with abnormal D- xylose absorption

	test or increased faecal fat excretion after exclusion of coeliac's disease (poor response to gluten-free diet) and gut vasculitis
60. Protein-losing enteropathy	diarrhoea with hypoalbuminaemia or increased faecal excretion of iv radiolabeled albumin after exclusion of gut vasculitis and malabsorption
61. Intestinal pseudo-obstruction	subacute intestinal obstruction due to intestinal hypomotility
62. Lupus hepatitis	raised transaminases
	absence of autoantibodies specific to autoimmune hepatitis (eg: anti-smooth muscle, anti-liver cytosol 1) &/or biopsy appearance of chronic active hepatitis
	hepatitis typically lobular with no piecemeal necrosis
	exclude drug-induced and viral hepatitis
63. Acute lupus cholecystitis	after exclusion of gallstones and infection
64. Acute lupus pancreatitis	usually associated multisystem involvement
OPHTHALMIC	
65. Orbital inflammation	orbital inflammation with myositis &/or extra-ocular muscle swelling &/or proptosis
	supportive imaging required
66. Severe keratitis	sight threatening includes: corneal melt peripheral ulcerative keratitis
67. Mild keratitis	not sight threatening
68. Anterior uveitis	
69. Severe posterior uveitis &/or retinal vasculitis	sight-threatening &/or retinal vasculitis not due to vaso-occlusive disease
70. Mild posterior uveitis &/or retinal vasculitis	not sight-threatening
	not due to vaso-occlusive disease
71. Episcleritis	
72. Severe scleritis	necrotising anterior scleritis

	anterior &/or posterior scleritis requiring systemic steroids/immunosuppression &/or not responding to NSAIDs
73. Mild scleritis	anterior &/or posterior scleritis not requiring systemic steroids excludes necrotising anterior scleritis
74. Retinal/choroidal vaso-occlusive disease	includes: retinal arterial & venous occlusion serous retinal &/or retinal pigment epithelial detachments secondary to choroidal vasculopathy
75. Isolated cotton-wool spots	also known as cytoid bodies
76. Optic neuritis	excludes anterior ischaemic optic neuropathy
77. Anterior ischaemic optic neuropathy	visual loss with pale swollen optic disc due to occlusion of posterior ciliary arteries
RENAL	
78. Systolic blood pressure 79. Diastolic blood pressure 80. Accelerated hypertension	blood pressure rising to > 170/110 mm Hg within 1 month with grade 3 or 4 Keith-Wagener-Barker retinal changes (flame-shaped haemorrhages or cotton-wool spots or papilloedema)
81. Urine dipstick 82. Urine albumin-creatinine ratio	on freshly voided urine sample conversion: 1 mg/mg = 113 mg/mmol it is important to exclude other causes (especially infection) when proteinuria is present
83. Urine protein-creatinine ratio	on freshly voided urine sample conversion: 1 mg/mg = 113 mg/mmol it is important to exclude other causes (especially infection) when proteinuria is present
84. 24 hour urine protein	it is important to exclude other causes (especially infection) when proteinuria is present
85. Nephrotic syndrome	criteria: heavy proteinuria (≥ 3.5 g/day or protein-

	creatinine ≥ 350 mg/mmol or albumin-creatinine ratio ≥ 350 mg/mmol) hypoalbuminaemia oedema
86. Plasma/Serum creatinine	exclude other causes for increase in creatinine (especially drugs)
87. GFR	MDRD formula: GFR = 170 x [serum creatinine (mg/dl)]$^{-0.999}$ x [age]$^{-0.176}$ x [serum urea (mg/dl)]$^{-0.17}$ x [serum albumin (g/dl)]$^{0.318}$ x [0.762 if female] x [1.180 if African ancestry] units = ml/min per 1.73 m^2 normal: male = 130 ± 40 female = 120 ± 40 conversion: serum creatinine - mg/dl = (µmol/l)/88.5 serum urea - mg/dl = (mmol/l) x 2.8 serum albumin - g/dl = (g/l)/10 creatinine clearance not recommended as it is not reliable exclude other causes for decrease in GFR (especially drugs)
88. Active urinary sediment	pyuria (> 5 WCC/hpf or > 10 WCC/mm^3 (µl)) OR haematuria (> 5 RBC/hpf or > 10 RBC/mm^3 (µl)) OR red cell casts OR white cell casts exclude other causes (especially infection, vaginal bleed, calculi)
89. Histology of active nephritis	WHO Classification (1995): (any one) Class III – (a) or (b) subtypes Class IV – (a), (b) or (c) subtypes Class V – (a), (b), (c) or (d) subtypes Vasculitis

	OR
	ISN/RPS Classification (2003): (any one) Class III – (A) or (A/C) subtypes Class IV – (A) or (A/C) subtypes Class V Vasculitis
	within last 3 months
	glomerular sclerosis without inflammation not included

HAEMATOLOGICAL

90. Haemoglobin	exclude dietary deficiency & GI blood loss
91. White cell count	exclude drug-induced cause
92. Neutrophil count	exclude drug-induced cause
93. Lymphocyte count	
94. Platelet count	exclude drug-induced cause
95. TTP	thrombotic thrombocytopaenic purpura
	clinical syndrome of micro-angiopathic haemolytic anaemia and thrombocytopenia in absence of any other identifiable cause
96. Evidence of active haemolysis	positive Coombs' test & evidence of haemolysis (raised bilirubin or raised reticulocyte count or reduced haptoglobulins or fragmented RBC or microspherocytes)
97. Isolated positive Coombs' test	

ADDITIONAL ITEMS

These items are required mainly for calculation of GFR

i. Weight
ii. African ancestry
iii. Serum urea
iv. Serum albumin

References:

1) Rule of nines diagram. Burn Center, University of Utah Health Sciences Center (http://uuhsc.utah.edu/burncenter/emergencycare/extent.html)

2) Levey, A. S., Bosch, J. P., Lewis, J. B., Greene, T., Rogers, N., & Roth, D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann.Intern.Med.* 1999; 130(6): 461-470.

3) Weening, J. J., D'Agati, V. D., Schwartz, M. M., Seshan, S. V., Alpers, C. E., Appel, G. B., Balow, J. E., Bruijn, J. A., Cook, T., Ferrario, F., Fogo, A. B., Ginzler, E. M., Hebert, L., Hill, G., Hill, P., Jennette, J. C., Kong, N. C., Lesavre, P., Lockshin, M., Looi, L. M., Makino, H., Moura, L. A., & Nagata, M. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J.Am.Soc.Nephrol.* 2004; 15(2): 241-250.

Appendix 14
British Isles Lupus Assessment Group (BILAG)-2004 Index Scoring

CONSTITUTIONAL

Category A:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **AND**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/splenomegaly
Anorexia

Category B:
Pyrexia recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any 2 or more of the following recorded as 2 (same), 3 (worse) or 4 (new):

Weight loss
Lymphadenopathy/splenomegaly
Anorexia

BUT do not fulfil criteria for Category A

Category C
Pyrexia recorded as 1 (improving) **OR**

One or more of the following recorded as > 0:

Weight loss
Lymphadenopathy/Splenomegaly
Anorexia

BUT does not fulfil criteria for category A or B

Category D
Previous involvement

Category E
No previous involvement

MUCOCUTANEOUS

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - severe
Angio-oedema - severe
Mucosal ulceration - severe
Panniculitis/Bullous lupus - severe
Major cutaneous vasculitis/thrombosis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Skin eruption - mild
Panniculitis/Bullous lupus - mild
Digital infarcts or nodular vasculitis
Alopecia - severe

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Angio-oedema - mild
Mucosal ulceration - mild
Alopecia - mild
Periungual erythema/chilblains
Splinter haemorrhages

Category D
Previous involvement

Category E
No previous involvement

NEUROPSYCHIATRIC

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Aseptic meningitis
Cerebral vasculitis
Demyelinating syndrome
Myelopathy
Acute confusional state
Psychosis
Acute inflammatory demyelinating polyradiculoneuropathy
Mononeuropathy (single/multiplex)
Cranial neuropathy
Plexopathy
Polyneuropathy
Status epilepticus
Cerebellar ataxia

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Seizure disorder
Cerebrovascular disease (not due to vasculitis)
Cognitive dysfunction
Movement disorder
Autonomic disorder
Lupus headache - severe unremitting
Headache due to raised intracranial hypertension

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

MUSCULOSKELETAL

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Severe Myositis
Severe Arthritis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Mild Myositis
Moderate Arthritis/Tendonitis/Tenosynovitis

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Mild Arthritis/Arthralgia/Myalgia

Category D
Previous involvement

Category E
No previous involvement

Appendix 14: BILAG-2004 Index Scoring

CARDIORESPIRATORY

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Myocarditis/Endocarditis + Cardiac failure
Arrhythmia
New valvular dysfunction
Cardiac tamponade
Pleural effusion with dyspnoea
Pulmonary haemorrhage/vasculitis
Interstitial alveolitis/pneumonitis
Shrinking lung syndrome
Aortitis
Coronary vasculitis

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Pleurisy/Pericarditis
Myocarditis - mild

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

Appendix 14: BILAG-2004 Index Scoring

GASTROINTESTINAL

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Peritonitis
Lupus enteritis/colitis
Intestinal pseudo-obstruction
Acute lupus cholecystitis
Acute lupus pancreatitis

Category B
Any Category A feature recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Abdominal serositis and/or ascites
Malabsorption
Protein losing enteropathy
Lupus hepatitis

Category C
Any Category B features recorded as 1 (improving)

Category D
Previous involvement

Category E
No previous involvement

OPHTHALMIC

Category A
Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Orbital inflammation/myositis/proptosis
Keratitis - severe
Posterior uveitis/retinal vasculitis - severe
Scleritis - severe
Retinal/choroidal vaso-occlusive disease
Optic neuritis
Anterior ischaemic optic neuropathy

Category B
Any Category A features recorded as 1 (improving) **OR**

Any of the following recorded as 2 (same), 3 (worse) or 4 (new):

Keratitis - mild
Anterior uveitis
Posterior uveitis/retinal vasculitis - mild
Scleritis - mild

Category C
Any Category B features recorded as 1 (improving) **OR**

Any of the following recorded as > 0:

Episcleritis
Isolated cotton-wool spots (cytoid bodies)

Category D
Previous involvement

Category E
No previous involvement

Appendix 14: BILAG-2004 Index Scoring

RENAL

Category A
Two or more of the following **providing 1, 4 or 5 is included**:

1. Deteriorating proteinuria (severe) defined as

   (a) urine dipstick increased by ≥ 2 levels (used only if other methods of urine protein estimation not available); **or**

   (b) 24 hour urine protein > 1 g that has not decreased (improved) by ≥ 25%; **or**
   (c) urine protein-creatinine ratio > 100 mg/mmol that has not decreased (improved) by ≥ 25%; **or**
   (d) urine albumin-creatinine ratio > 100 mg/mmol that has not decreased (improved) by ≥ 25%

2. Accelerated hypertension
3. Deteriorating renal function (severe) defined as

   (a) plasma creatinine > 130 μmol/l and having risen to > 130% of previous value; **or**
   (b) GFR < 80 ml/min per 1.73 m^2 and having fallen to < 67% of previous value; **or**
   (c) GFR < 50 ml/min per 1.73 m^2, and last time was > 50 ml/min per 1.73 m^2 or was not measured.

4. Active urinary sediment
5. Histological evidence of active nephritis within last 3 months
6. Nephrotic syndrome

Category B
One of the following:

1. One of the Category A feature

2. Proteinuria (that has not fulfilled Category A criteria)
   (a) urine dipstick which has risen by 1 level to at least 2+ (used only if other methods of urine protein estimation not available); **or**

   (b) 24 hour urine protein ≥ 0.5 g that has not decreased (improved) by ≥ 25%; **or**
   (c) urine protein-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥ 25%; **or**
   (d) urine albumin-creatinine ratio ≥ 50 mg/mmol that has not decreased (improved) by ≥ 25%

3. Plasma creatinine > 130 μmol/l and having risen to ≥ 115% but ≤ 130% of previous value

Category C
One of the following:

1. Mild/Stable proteinuria defined as

(a) urine dipstick ≥ 1+ but has not fulfilled criteria for Category A & B (used only if other methods of urine protein estimation not available); **or**
(b) 24 hour urine protein > 0.25 g but has not fulfilled criteria for Category A & B ; **or**
(c) urine protein-creatinine ratio > 25 mg/mmol but has not fulfilled criteria for Category A & B; **or**
(d) urine albumin-creatinine ratio > 25 mg/mmol but has not fulfilled criteria for Category A & B

2. Rising blood pressure (providing the recorded values are > 140/90 mm Hg) which has not fulfilled criteria for Category A & B, defined as

(a) systolic rise of ≥ 30 mm Hg; **and**
(b) diastolic rise of ≥ 15mm Hg

Category D
Previous involvement

Category E
No previous involvement

Note: although albumin-creatinine ratio and protein-creatinine ratio are different, we use the same cut-off values for this index

Appendix 14: BILAG-2004 Index Scoring

HAEMATOLOGICAL

Category A

TTP recorded as 2 (same), 3 (worse) or 4 (new) **OR**

Any of the following:

Evidence of haemolysis and Haemoglobin	< 8 g/dl
Platelet count	< 25 **x** 10^9/l

Category B
TTP recorded as 1 (improving) **OR**

Any of the following:

Evidence of haemolysis and Haemoglobin	8 - 9.9 g/dl
Haemoglobin	< 8 g/dl (without haemolysis)
White cell count	< 1.0 **x** 10^9/l
Neutrophil count	< 0.5 **x** 10^9/l
Platelet count	25 - 49 **x** 10^9/l

Category C
Any of the following:

Evidence of haemolysis and Haemoglobin	≥ 10g/dl
Haemoglobin	8 - 10.9 g/dl (without haemolysis)
White cell count	1 - 3.9 **x** 10^9/l
Neutrophil count	0.5 - 1.9 **x** 10^9/l
Lymphocyte count	< 1.0 **x** 10^9/L
Platelet count	50 - 149 **x** 10^9/l
Isolated Coombs' test positive	

Category D
Previous involvement

Category E
No previous involvement

Operational Issues

1) For Renal and Haematological item to score the corresponding 'Attributable to SLE Activity' flag must be set to 'YES'

2) Missing Items

If a field is left blank then the item value from the previous assessment is 'carried forward' and is used in scoring. The previous value will appear in the Calculation value field.

3) Attributable to SLE Activity

If a field has an associated 'Attributable To SLE Activity' flag which is set to 'YES' then the Data Entry value is copied to the Calculation field and is used in the scoring.

If a field has an 'Attributable To SLE Activity' flag which is set to 'NO', the Data Entry value is preserved in the Data Entry field, but the value is not used in the calculation of the score. If the 'Attributable to SLE Activity' flag is set to 'NO' then the item value from the previous assessment is 'carried forward' and is used in scoring. The previous value will appear in the Calculation value field. This mechanism ensures that a falsely low score is not achieved through missing values. Values which are NOT attributable to SLE activity remain in the assessment and are NOT carried forward for scoring purposes.

4) Proteinuria Equivalence

For the purposes of interchangeability between different Proteinuria measurements, a unit of Proteinuria Equivalence (g) has been adopted:

1g of Urinary Protein = 100mg/mmol Protein:Creatinine ratio = 100mg/mmol Albumin:Creatinine ratio

In the event that more than one measurement is entered the 24 hr Urinary Protein takes precedence over the Protein:Creatinine ratio, which in turn takes precedence over Albumin:Creatinine ratio. Urinary Dipstick will only be scored if the three Proteinuria measurements are all blank.

5) Renal rescoring

Renal scoring involves comparison with the previous assessment. It is permissible to change a Renal score at anytime, but it requires that all SUBSEQUENT Renal assessments for the patient are rescored also, regardless of whether the Renal (A,B, C, D, E) score changes. There is no need to rescore assessments which are prior to the changed assessment.

Appendix 15
Physician's Global Assessment of Disease Activity (PGA)

(Sample; Not to Be Used to Enter Subject Data)

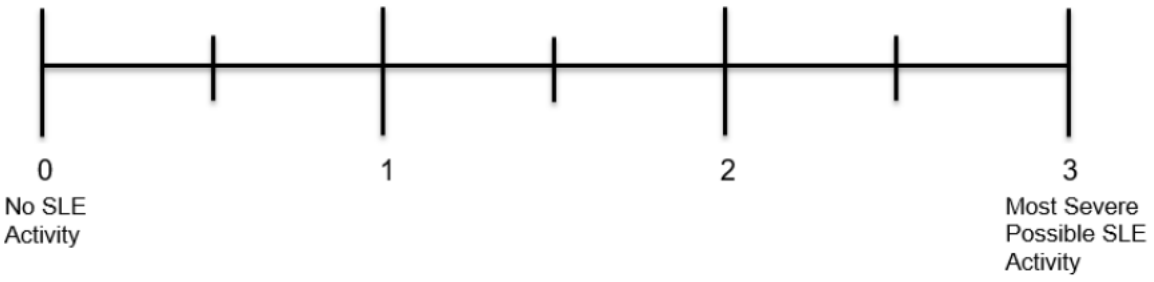
Please answer the following question by placing a **vertical mark through the line below**.

Please provide a global assessment of the patient's overall SLE disease severity over the past 4 weeks. The PGA is scored from 0 (no SLE activity) to 3 (the most severe SLE activity) on a VAS scale. Specific guidance on PGA values is given below.

PGA Score	Interpretation
3	The most severe possible SLE activity in any SLE participant, This score is very rare.
>2.5	Severe SLE activity, This typically warrants urgent treatment with highly active therapies.
2	Moderate SLE activity
1	Mild SLE disease activity
0	No SLE activity

SLE = systemic lupus erythematosus; PGA = Physician's Global Assessment.

When scoring PGA, the score from the previous visit must be reviewed first, and the score for the present visit must be assigned relative to the previous visit's disease.



Site Measurement: _____mm

Appendix 16
Subject's Global Assessment of Disease Activity (SGA)

(Sample; Not to Be Used to Enter Subject Data)

SUBJECT'S GLOBAL ASSESSMENT (SCREENING)

Check if assessment was not done: ☐

Please answer the following question by placing a **vertical mark through the line**.

Global Assessment of Disease Activity

On the line below, considering all the ways your Lupus affects you, where would you rate your Lupus symptoms over the last 10 days?

None _____ Severe

Site Measurement: °_____ mm

Use the original document provided by sponsor
Do not photocopy the document since this may alter the length of the 100 mm line

Appendix 17
Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) Scale

(Sample; Not to Be Used to Enter Subject Data)

FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble starting things because I am tired	0	1	2	3	4
An4	I have trouble finishing things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

English (Universal)
Copyright 1987, 1997

Appendix 18
36-Item Short Form Survey (SF-36) (Version 2, Acute)

(Sample; Not to Be Used to Enter Subject Data)

SF-36 Acute Version

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐1	☐2	☐3	☐4	☐5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
	▼	▼	▼
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐1	☐2	☐3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐1	☐2	☐3
c. Lifting or carrying groceries	☐1	☐2	☐3
d. Climbing several flights of stairs	☐1	☐2	☐3
e. Climbing one flight of stairs	☐1	☐2	☐3
f. Bending, kneeling, or stooping	☐1	☐2	☐3
g. Walking more than a mile	☐1	☐2	☐3
h. Walking several hundred yards	☐1	☐2	☐3
i. Walking one hundred yards	☐1	☐2	☐3
j. Bathing or dressing yourself	☐1	☐2	☐3

4. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Were limited in the kind of work or other activities	☐1	☐2	☐3	☐4	☐5
d. Had difficulty performing the work or other activities (for example, it took extra effort)	☐1	☐2	☐3	☐4	☐5

5. **During the past week, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?**

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	☐1	☐2	☐3	☐4	☐5
b. Accomplished less than you would like	☐1	☐2	☐3	☐4	☐5
c. Did work or other activities less carefully than usual	☐1	☐2	☐3	☐4	☐5

6. **During the past week, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

7. **How much bodily pain have you had during the past week?**

None	Very mild	Mild	Moderate	Severe	Very Severe
☐1	☐2	☐3	☐4	☐5	☐6

8. During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you during the past week. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past week:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐1	☐2	☐3	☐4	☐5
b. Have you been very nervous?	☐1	☐2	☐3	☐4	☐5
c. Have you felt so down in the dumps that nothing could cheer you up?	☐1	☐2	☐3	☐4	☐5
d. Have you felt calm and peaceful?	☐1	☐2	☐3	☐4	☐5
e. Did you have a lot of energy?	☐1	☐2	☐3	☐4	☐5
f. Have you felt downhearted and depressed?	☐1	☐2	☐3	☐4	☐5
g. Did you feel worn out?	☐1	☐2	☐3	☐4	☐5
h. Have you been happy?	☐1	☐2	☐3	☐4	☐5
i. Did you feel tired?	☐1	☐2	☐3	☐4	☐5

10. During the past week, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐1	☐2	☐3	☐4	☐5
b. I am as healthy as anybody I know	☐1	☐2	☐3	☐4	☐5
c. I expect my health to get worse	☐1	☐2	☐3	☐4	☐5
d. My health is excellent	☐1	☐2	☐3	☐4	☐5

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(SF-36v2 Acute, US Version 2.0)

THANK YOU FOR COMPLETING THESE QUESTIONS!

Appendix 19
Cutaneous Lupus Erythematosus Disease Area and Severity (CLASI)

(Sample; Not to Be Used to Enter Subject Data)

Cutaneous LE Disease Area and Severity Index (CLASI)

Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion

	activity		damage		
Anatomical Location	Erythema	Scale/ Hypertrophy	Dyspigmentation	Scarring/ Atrophy/ Panniculitis	Anatomical Location
	0-absent 1-pink; faint erythema 2- red; 3-dark red; purple/violaceous/ crusted/ hemorrhagic	0-absent; 1-scale 2-verrucous/ hypertrophic	0-absent, 1-dyspigmentaton	0 – absent 1 – scarring 2 – severely atrophic scarring or panniculitis	
Scalp				See below	Scalp
Ears					Ears
Nose (incl. malar area)					Nose (incl. malar area)
Rest of the face					Rest of the face
V-area neck (frontal)					V-area neck (frontal)
Post. Neck &/or shoulders					Post. Neck &/or shoulders
Chest					Chest
Abdomen					Abdomen
Back, buttocks					Back, buttocks
Arms					Arms
Hands					Hands
Legs					Legs
Feet					Feet

Mucous membrane

Mucous membrane lesions (examine if patient confirms involvement)	
0-absent; 1-lesion or ulceration	

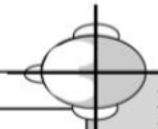
Dyspigmentation

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient – tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

Alopecia



Recent Hair loss (within the last 30 days / as reported by patient) 1-Yes 0-No	

NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

Alopecia (clinically not obviously scarred)		Scarring of the scalp (judged clinically)	
0-absent 1-diffuse; non-inflammatory 2-focal or patchy in one quadrant; 3-focal or patchy in more than one quadrant		0- absent 3- in one quadrant 4- two quadrants 5- three quadrants 6- affects the whole skull	

Total Activity Score
(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia)

Total Damage Score
(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp)

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Appendix 20
EuroQol 5-Dimension Questionnaire, 5-Level Version (EQ-5D-5L)

(Sample; Not to Be Used to Enter Subject Data)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ☐
I have slight problems walking ☐
I have moderate problems walking ☐
I have severe problems walking ☐
I am unable to walk ☐

SELF-CARE

I have no problems washing or dressing myself ☐
I have slight problems washing or dressing myself ☐
I have moderate problems washing or dressing myself ☐
I have severe problems washing or dressing myself ☐
I am unable to wash or dress myself ☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ☐
I have slight problems doing my usual activities ☐
I have moderate problems doing my usual activities ☐
I have severe problems doing my usual activities ☐
I am unable to do my usual activities ☐

PAIN / DISCOMFORT

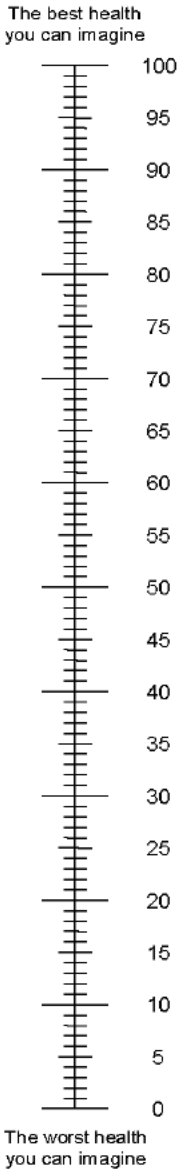
I have no pain or discomfort ☐
I have slight pain or discomfort ☐
I have moderate pain or discomfort ☐
I have severe pain or discomfort ☐
I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

I am not anxious or depressed ☐
I am slightly anxious or depressed ☐
I am moderately anxious or depressed ☐
I am severely anxious or depressed ☐
I am extremely anxious or depressed ☐

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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Appendix 21
Investigational Medicinal Product and Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Obinutuzumab (RO5072759)	IMP (test product)	Authorized	No
RO5072759 placebo	IMP (placebo)	Unauthorized	Not applicable
Methylprednisolone	AxMP (premedication)	Authorized	Yes
Acetaminophen/ Paracetamol	AxMP (premedication)	Authorized	Yes
Diphenhydramine hydrochloride	AxMP (premedication)	Authorized	Yes

AxMP =auxiliary medicinal product; EEA =European Economic Area; IMP =investigational medicinal product.

Table 2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom

Product Name	IMP/NIMP Designation	Marketing Authorization Status in UK	Used within Marketing Authorization
Obinutuzumab (RO5072759)	IMP (test product)	Authorized	No
RO5072759 placebo	IMP (placebo)	Unauthorized	Not applicable
Methylprednisolone	NIMP (premedication)	Authorized	Yes
Acetaminophen/ Paracetamol	NIMP (premedication)	Authorized	Yes
Diphenhydramine hydrochloride	NIMP (premedication)	Authorized	Yes

IMP =investigational medicinal product; NIMP =non-investigational medicinal product.

Appendix 22
Protocol Amendment History

A rationale for the current amendment precedes the Table of Contents.

PROTOCOL AMENDMENT, VERSION 3: 10 MAY 2023

Protocol CA42750, Version 3, has been amended to reflect the increase in study sample size and to clarify elements related to certain study procedures. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- The study schema has been updated to reflect the increased sample size (Section 1.2).
- The assessment of interactive voice or web-based response system (IxRS) at Week 52 (Day 364) during the blinded treatment period has been added (Section 1.3, Table 1).
- The assessment of ECG at Week 104 (on Day 728) during the open-label treatment period has been removed (Section 1.3, Table 2).
- The assessment of vaccination antibody titers has been added at early study discontinuation visit during the open-label treatment period (Section 1.3, Table 2).
- Several objectives initially listed as exploratory objectives have been moved to other secondary objectives to better reflect how patients feel, function, and survive (Section 3, Table 4).
- An endpoint reflecting achievement of remission (DORIS) has been added to other secondary objectives to further describe how patients feel, function, and survive (Section 3, Table 4).
- The endpoint, proportion of participants who achieve SRI(8) at Week 52, has been moved from other secondary objectives to exploratory objectives (Section 3, Table 4).
- The duplicated exploratory objectives pertaining to improvement on the tender/swollen joint count and Cutaneous Lupus Erythematosus Disease Area and Severity (CLASI) forms have been removed as these two objectives were inadvertently duplicated initially (Section 3, Table 4).
- A section describing patient input into the study design has been added to align with Clinical Trial Regulation (CTR) requirements (Section 4.1.7).
- The protocol has been updated throughout to reflect the increase in study sample size from approximately 200 to 300 participants, which will bolster the statistical power to greater than 90% for meeting the primary efficacy endpoint and further increase the power for the key secondary endpoints (Sections 5 and 9).
- The contraception requirement has been modified to reflect the exact wording of the Investigator's Brochure changing from "two contraception methods with a failure rate $<1\%$ per year" to "adequate contraceptive method" (Section 5.1).

- The requirement to wait at least 3 hours after a meal for ECG assessment has been removed due to lack of clinical rationale and to reduce burden on the participant (Section 8.2.3).
- It has been clarified that only systemic infusion-related reactions should be considered as adverse events of special interest (Section 8.3.8).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitors has been removed from the protocol (front matter and Section 8.3.9). Medical Monitor contact information has been replaced with a sentence indicating that this information will be provided separately to sites.
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 8.11.1.6).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section A1-4).
- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section A1-6).
- The Sponsor record retention policy has been clarified (Section A1-7).
- Autoantibody profile and complements have been removed from central laboratory tests as these are considered biomarkers and not safety assessments (Appendix 2).
- Collection of serum samples for immunogenicity testing in the event of a suspected anaphylactic reaction during study treatment administration has been removed as serum sample is already collected prior to study treatment administration (Appendix 7).
- Deflazacort has been added to the corticosteroid equivalence chart following requests from several countries that use this corticosteroid (Appendix 10).

PROTOCOL AMENDMENT, VERSION 2: 31 MARCH 2022

Protocol CA42750, Version 2, has been amended to address recommendations from the U.S. Food and Drug Administration (FDA), to provide updated Medical Monitor and contact information, and to clarify elements related to certain study procedures. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- Language referencing the approval, confirmation, or verification by the Medical Monitor has been removed throughout the document in accordance with Sponsor guidelines, and to ensure that protocol guidance clearly indicates that interactions with the Medical Monitor are driven by the investigator.

- The schedules of activities have been revised to reflect the following changes (Section 1.3, Tables 1 and 2):
  - The study day for the last day of the screening period has been clarified and updated from 0 to -1 (Table 1).
  - Study Day 210 has been changed to Study Day 196 to correct a typographical error (Table 1).
  - A note was added to clarify that all assessments should be performed before any medications, including premedications, are administered unless otherwise specified (Table 1 and Table 2).
  - The requirement that informed consent must be documented before any study-specific screening procedure is performed has been clarified (Table 1, footnote “a”).
  - The Unscheduled Visit column has been updated with a footnote clarifying assessments at unscheduled visits (Table 1, footnote “b” and Table 2, footnote “a”).
  - Additional information has been included regarding the requirements for completion of systemic lupus erythematosus (SLE) disease activity assessments for clinician-reported outcomes, which include tender/swollen joint counts, Cutaneous and Lupus Erythematosus Disease Area and Severity, Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), British Isles Lupus Assessment Group 2004 (BILAG-2004) Index, and Physician’s Global Assessment, during screening and at subsequent visits (Table 1, footnote “d”).
  - The type of pregnancy testing has been clarified during blinded and open-label treatment and requires a negative urine (rather than serum) pregnancy test at screening and prior to all study drug infusions (Table 1, footnote “l” and Table 2, footnote “j").
  - To improve participant experience and to reduce site burden without affecting data interpretation, the wording pertaining to the timing of pharmacokinetic (PK) sampling has been updated during blinded and open-label treatment (Table 1, footnote “q” and Table 2, footnote “p”).
  - The urine biomarker sample has been removed, given that urinalysis alone will be sufficient to characterize treatment-associated changes (Table 1, footnote “r” and Table 2, footnote “q,” and Sections 8.7 and 8.11.1.3).
- The background section on SLE has been updated to reflect the approval of a second medication for the treatment of SLE (Section 2.2.1).
- Language related to a benefit–risk assessment of study treatment in the setting of the coronavirus 2019 (COVID-19) pandemic and the impact of COVID-19 vaccines has been added (Section 2.3).

- The oral corticosteroid dose-reduction threshold has been changed from 5 mg/day to 7.5 mg/day for the two secondary endpoints focused on steroid reduction in Table 4 to more closely align with consensus guidelines, and an exploratory endpoint regarding the proportion of participants achieving prednisone doses $\leq$ 5 mg/day sustained from Week 40 – Week 52 has been added (Section 3).
- The secondary endpoint focused on time to first BILAG flare at 52 weeks has been rearranged to a key secondary endpoint from its previous position within 'other secondary endpoints' in Table 4 to reflect its position as a more relevant clinical and patient-related endpoint (Section 3).
- The sources supplying premedications have been updated to accurately reflect the supplier, and the intravenous administration option has been added for the premedications previously listed as by mouth only in Table 5 to allow sites greater flexibility (Sections 4.1.2, 4.1.3, and 6.1).
- Details about modifications to SLEDAI-2K scoring for determination of eligibility have been reorganized for clarity (Section 5.1).
- The description of screen failures has been revised to align with Roche's global data standards (Section 5.4).
- The instructions outlining investigator recording of participants who are screened to document eligibility or record reasons for screen failure have been clarified (Sections 5.4 and 8).
- The SLEDAI-2K score stratification factor has been updated to use the SLEDAI-2K score determined at screening instead of the score at baseline, given that the Day 1 SLEDAI-2K score cannot be determined until laboratory results from the Day 1 visit are available (Sections 6.3.1).
- Guidance pertaining to corticosteroid bursts has been revised for clarity; additionally, new language details that after Week 12, administration of corticosteroid burst or oral corticosteroid doses exceeding baseline dose requires Medical Monitor notification (Section 6.8.1.3).
- Guidance pertaining to the mandatory oral corticosteroid (OCS) taper has been updated to include a requirement to initiate OCS taper in eligible participants within 14 days of the visit, as well as a requirement for Medical Monitor notification if OCS taper is not attempted in clinically eligible participants (Section 6.8.1.4).
- Section 6.8.4, Premedication for Infusions, has been deleted to avoid redundancy in the protocol (Section 6.8.4) and subsequent sections have been renumbered accordingly.
- Language has been modified to clarify the conditions in which participants will be considered to have experienced treatment failure (Section 6.8.4).
- Bisphosphonate therapy and COVID-19 vaccination have been added to the list of permitted therapies (Section 6.8.5).

- Language was added to clarify that participants must permanently discontinue study treatment if they receive rescue medication (Section 7.1).
- In response to health authority feedback, language has been clarified to indicate that the only reason for a participant to be considered withdrawn from the study is due to withdrawal of consent, and the decision to discontinue a participant from the study is at the discretion of the investigator (Section 7.2).
- Language has been clarified to indicate that laboratory-based items will reflect the central laboratory results obtained at the same visit for which SLEDAI-2K and BILAG-2004 Index are completed (Section 8.1.1 and Section 8.1.2).
- The expectations for the performance of BILAG-2004 assessments, which requires an additional step during screening only (assignment of domain-specific Category A and/or B severity grades to applicable domains), as well as additional details on how to complete the BILAG-2004 Index correctly at subsequent visits, have been clarified (Section 8.1.2).
- The names of the Serious Adverse Event Reporting Form and the Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Form have been changed to Clinical Trial Adverse Event/Special Situations Form (Section 8.3.1 and Appendix 3, Sections A3-4.1, 4.2, 5.1, 5.2, and 6).
- The primary and secondary Medical Monitors have been replaced, and the new primary and secondary Medical Monitors' names and emergency medical contact information have been updated accordingly (Section 8.3.9).
- The table describing analysis sets was updated to provide additional details on the safety-evaluable and PK-evaluable analysis sets, and the definition of the efficacy-evaluable set was revised to clarify that all efficacy analyses will be performed using the modified intent-to-treat population (Section 9.3).
- Details of statistical analyses have been revised to reflect an updated approach, specifically with regard to imputation strategy and the definition of intercurrent events, based on health authority feedback (Section 9.4).
- References have been updated based on changes made to the protocol (Section 10).
- Language has been clarified in Appendix 1, Section A1-1 to indicate that any substantial amendments to the protocol will require Institutional Review Board/Ethics Committee and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants (Appendix 1, Section A1-1).
- Language has been modified to clarify that patients who are re-screened are not required to sign another Informed Consent Form if the re-screening occurs within 35 days (Appendix 1, Section A1-3).

- The serum sample for quantitative IgE has been removed from the list of clinical safety laboratory tests as this is not necessary for safety monitoring, and additional local and central laboratory tests have been added (Appendix 2, Table 1).
- The title of the “Contraceptive Guidance and Collection of Pregnancy Information” appendix has been changed to “Collection of Pregnancy Information,” as the information regarding contraception is already described in the Inclusion Criteria (Section 5.1), and only the part on data collection remains in Appendix 4. Additional wording related to collection of pregnancy information is also included in this amendment (Appendix 4).
- The recently identified potential risk of coagulation abnormalities, including the risks of disseminated intravascular coagulation, has been added to the list of potential risks associated with obinutuzumab (Appendix 6).
- Table 2 has been updated to clarify the timing of particular measurements in the case of a serious infectious adverse event (Appendix 6).
- Table 2 has been updated to reference and link to the appropriate tables within the same section detailing infusion guidelines, and a bullet point has been added to ensure that, in the event of an infusion-related reaction, a slower infusion rate is to be maintained for 30 minutes before re-increasing the rate to align with most recent safety guidance (Appendix 9).
- Meprednisone has been added to the corticosteroid equivalence chart following requests from several countries that use this corticosteroid (Appendix 10).
- The complete BILAG-2004 Index Glossary was inadvertently omitted from Version 1 of the protocol and has been inserted to assist in correct, accurate, and consistent completion of the BILAG-2004 Index (Appendix 13).

Appendix 23
Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ADA	anti-drug antibody
AE	adverse events
ANA	anti-nuclear antibody
ANCOVA	analysis of covariance
AUC	area under the concentration–time curve
AxMP	auxiliary medicinal product
BICLA	British Isles Lupus Assessment Group-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
BTK	Bruton's tyrosine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CLASI	Cutaneous Lupus Erythematosus Disease Area and Severity
ClinRO	clinician-reported outcome
CLL	chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus 2019
CRR	complete renal response
DRB	Data Review Board
DIC	disseminated intravascular coagulation
dsDNA	double-stranded DNA
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EQ-5D-5L	EuroQol 5-Dimension, 5-Level Questionnaire
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy–Fatigue
FDA	(U.S.) Food and Drug Administration
FL	follicular lymphoma
GFR	glomerular filtration rate
GI	gastrointestinal

Appendix 23: Abbreviations

Abbreviation	Definition
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HSFC	high-sensitivity flow cytometry
ICH	International Council for Harmonisation
iDCC	independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
IRR	infusion-related reaction
IxRS	interactive web response system
JAK	Janus-associated kinase
LLDAS	Lupus Low Disease Activity State
LLN	lower limit normal
LN	lupus nephritis
LPLV	last participant, last visit
MMF	mycophenolate mofetil
MN	mobile nursing
mITT	modified intent-to-treat
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	non-Hodgkin lymphoma
NIMP	non-investigational medicinal products
NK	natural killer
NSAID	nonsteroidal anti-inflammatory drug
OCS	oral corticosteroid
OLT	open-label treatment
PD	pharmacodynamic
PGA	Physician’s Global Assessment
PK	pharmacokinetic

Appendix 23: Abbreviations

Abbreviation	Definition
PO	by mouth
PML	progressive multifocal leukoencephalopathy
PRO	patient-reported outcome
PT	preferred term
QD	once a day
RBR	Research Biosample Repository
RNP	ribonucleoprotein
SAP	Statistical Analysis Plan
SF-36 v2	36-Item Short Form Survey, Version 2
SFU	study follow-up
SGA	Subject's Global Assessment
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index 2000
Sm	Smith
SOC	system organ class
SRI	Systemic Lupus Erythematosus Responder Index
SSA (Ro)	Sjogren's syndrome A
SSB (La)	Sjogren's syndrome B
TB	tuberculosis
TYK2	tyrosine kinase 2
ULN	upper limit of normal
UPCR	urinary protein-to-creatinine ratio
VAS	Visual Analog Scale
WES	whole exome sequencing
WGS	whole genome sequencing

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